UCONAP/226/US

NOVEL PYRAZOLE ANALOGS ACTING ON CANNABINOID RECEPTORS

Cross Reference to Related Applications

This application is a continuation-in-part of International Application No. PCT/US02/27644, filed August 29, 2002, which claims the benefit of United States Provisional Application No. 60/316,515, filed August 31, 2001, the contents of each of which are herein incorporated by reference in their entirety.

Field of the Invention

The present invention relates generally to biologically active pyrazole analogs capable of interacting with the CB1 and/or the CB2 cannabinoid receptors. One aspect of the invention is concerned with new and improved pyrazole analogs acting as antagonists for the CB1 and/or the CB2 receptors. Another aspect of the invention is concerned with new and improved pyrazole analogs having selectivity for the CB1 or CB2 cannabinoid receptor. Still other aspects of the invention are concerned with pharmaceutical preparations employing the inventive analogs and methods of administering therapeutically effective amounts of the inventive analogs to provide a physiological effect.

Background of the Invention

The classical cannabinoid Δ^9-Tetrahydrocannabinol (Δ^9-THC) is the major active constituent extracted from Cannabis sativa. The effects of such cannabinoids are due to an interaction with specific high-affinity receptors. Presently, two cannabinoid receptors have been characterized: CB1, a central receptor found in the mammalian brain and a number of other sites in peripheral tissues; and CB2, a peripheral receptor found principally in cells related to the immune system. The CB1 receptor is believed to mediate the psychoactive properties associated with classical cannabinoids. Characterization of these receptors has been made possible by the development of specific synthetic ligands such as the agonists WIN 55212-2 and CP 55,940.

In addition to acting at the cannabinoid receptors, cannabinoids such as Δ^9-THC also affect cellular membranes, thereby producing undesirable side effects such as drowsiness, impairment of monoamine oxidase function and impairment

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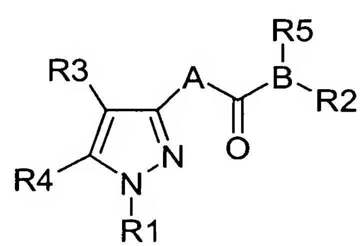
of non-receptor mediated brain function. The addictive and psychotropic properties of some cannabinoids also limit their therapeutic value.

U.S. Patent No. 6,028,084 describes some pyrazole derivatives alleged to have binding affinity for the central cannabinoid receptor. International Publication Number WO 01/29007A1 also describes some pyrazole derivatives having binding affinity for cannabinoid receptors.

The pharmacological effects of cannabinoids pertain to a variety of areas such as the central nervous system, the cardiovascular system, the immune system and/or endocrine system. Compounds possessing an affinity for the CB1 and/or the CB2 cannabinoid receptors are useful as agents acting on the central nervous system and in a variety of other roles.

Summary of the Invention

Briefly stated, one aspect of the invention is concerned with new and improved cannabimimetic (cannabinoid like) pyrazole analogs. The inventive cannabimimetic pyrazole ligands of this aspect can be represented by general formula I:



I

A comprises a direct bond, O or $-(CH_2)_lN(R6)-$,

R6 comprises hydrogen or a C1 to C6 alkyl, and

l is an integer from 0 to about 1.

B comprises N or O.

R1 comprises $-(CH_2)_n-Z$.

n is an integer from 0 to about 7.

Z comprises H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, O-acyl, O-aroyl, $O(CH_2)_dOH$, $O(CH_2)_dNX_1X_2$, NH-acyl, NH-aroyl, CHO, CF_3, $COOX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, alkoxy, alkylmercapto, alkylamino or di-alkylamino.

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X2 together comprise part of an imide ring having about 5 to about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl or alkyl-NX_1X_2.

d is an integer from 0 to about 6.

In a variation of the invention, R1 comprises $-(CH_2)_n-Z$.

n is an integer from 0 to about 7.

Z comprises a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring, a heteropolycyclic ring; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom.

In a variation of the invention, R1 comprises $-(CH_2)_n-Z$.

n is an integer from 0 to about 7.

Z comprises a 5 member unsaturated ring having 0 to 4 independently selected heteroatoms as ring members, a substituted 5

member unsaturated ring having 0 to 4 independently selected heteroatoms as ring members, a 6 member aromatic ring having 0 to 5 independently selected heteroatoms as ring members or a substituted 6 member aromatic ring having 0 to 5 independently selected heteroatoms; and wherein the connecting point between the -$(CH_2)_n$- group and the Z group can be any available ring carbon atom or any available ring nitrogen atom.

In a variation of the invention, R1 comprises $-(CH_2)_n-Z$.

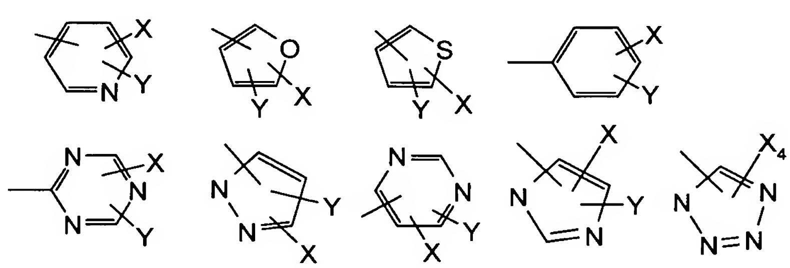
n is an integer from 0 to about 7.

Z comprises 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidinyl, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the -$(CH_2)_n$- group and the Z group can be any available ring carbon atom or any available ring nitrogen atom.

In a variation of the invention, R1 comprises $-(CH_2)_n-Z$.

n is an integer from 0 to about 7.

Z comprises



wherein X and Y each independently comprise H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, O-acyl, O-aroyl, NH-acyl, NH-aroyl, CHO, CF_3, $COOX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl, alkylsulfonyl or (when Z comprises a structure having two adjacent carbon atoms methylene dioxy.

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or

X_1 and X2 together comprise part of an imide ring having about 5 to about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl or alkyl-NX_1X_2.

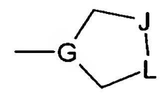
X_4 comprises H or alkyl.

In a variation of the invention, R1 comprises a carbocyclic ring having 6 ring atoms fused to a heterocyclic ring having from 5 to 7 ring atoms, a carbocyclic ring having 6 ring atoms fused to a heteroaromatic ring having from 5 to 7 ring atoms, a heterocyclic ring having 6 ring atoms fused to a heterocyclic ring having from 5 to 7 ring atoms, an heterocyclic ring having 6 ring atoms fused to a heteroaromatic ring having from 5 to 7 ring atoms, an aromatic ring having 6 ring atoms fused to a heterocyclic ring having from 5 to 7 ring atoms, an aromatic ring having 6 ring atoms fused to a heteroaromatic ring having from 5 to 7 ring atoms, a heteroaromatic ring having 6 ring atoms fused to a heterocyclic ring having from 5 to 7 ring atoms or a heteroaromatic ring having 6 ring atoms fused to a heteroaromatic ring having from 5 to 7 ring atoms.

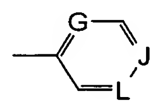
In any of the above R1 variations R1 can not be H when A is a direct bond and B is N.

R2 comprises a carbocyclic ring having about 4 to about 7 members, a heterocyclic ring having about 4 to about 7 members, an aromatic ring having

about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring or a heteropolycyclic ring.

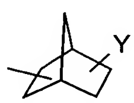
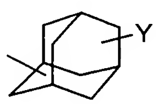
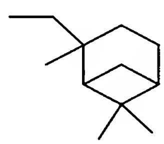
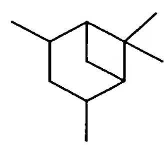
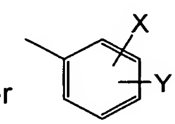
In a variation of the invention, R2 comprises 

wherein G comprises CH or N, and L and J each independently comprise $(CH_2)_n$, O, NH or S. n is an integer from 0 to about 7.

In a variation of the invention, R2 comprises 

wherein G, L and J each independently comprise CH or N.

In a variation of the invention, R2 comprises

, , ,  or 

wherein X and Y each independently comprise H, halogen, N_3, NCS, Ph (phenyl), CN, NO_2, NX_1X_2, OX_3, OAc, O-acyl, O-aroyl, NH-acyl, NH-aroyl, CHO, CF_3, $COOX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, alkyl, alcohol, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl or alkylsulfonyl.

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally a second heteroatom selected from O, N or S, or

X_1 and X2 together comprise part of an imide ring having about 5 to about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl or alkyl-NX_1X_2.

In a variation of the invention, R2 comprises a carbocyclic ring having 6 ring atoms fused to a heterocyclic ring having from 5 to 7 ring atoms, a carbocyclic ring having 6 ring atoms fused to a heteroaromatic ring having from 5 to 7 ring atoms, a heterocyclic ring having 6 ring atoms fused to a heterocyclic ring having from 5 to 7 ring atoms, an heterocyclic ring having 6 ring atoms fused to a heteroaromatic ring having from 5 to 7 ring atoms, an aromatic ring having 6 ring atoms fused to a heterocyclic ring having from 5 to 7 ring atoms, an aromatic ring having 6 ring atoms fused to a heteroaromatic ring having from 5 to 7 ring atoms, a heteroaromatic ring having 6 ring atoms fused to a heterocyclic ring having from 5 to 7 ring atoms or a heteroaromatic ring having 6 ring atoms fused to a heteroaromatic ring having from 5 to 7 ring atoms.

R3 comprises H, halogen, N_3, NCS, Ph, CN, NO_2, NX_1X_2, OX_3, OAc, O-acyl, O-aroyl, $O(CH_2)_dOH$, $O(CH_2)_dNX_1X_2$, NH-acyl, NH-aroyl, CHO, CF_3, $COOX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, alkyl, alcohol, alkoxy, alkylmercapto, alkylamino or di-alkylamino, alkylsulfinyl or alkylsulfonyl.

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally a second heteroatom selected from O, N or S, or

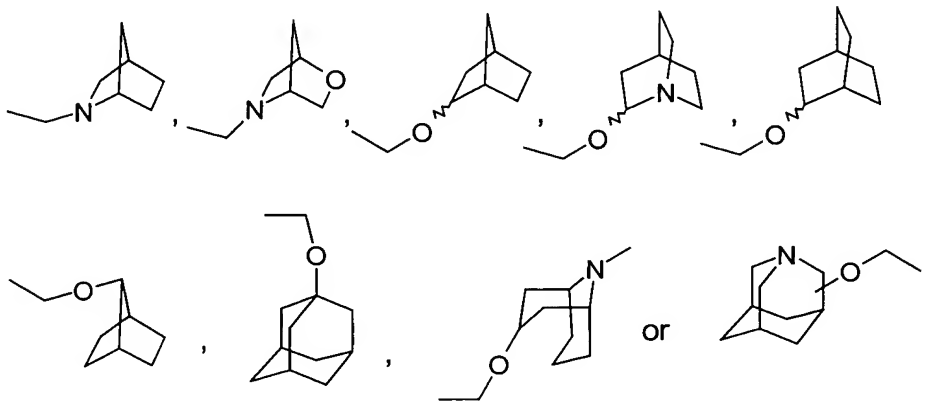
X_1 and X2 together comprise part of an imide ring having about 5 to about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl or alkyl-NX_1X_2.

d is an integer from 0 to about 6.

In a variation of the invention, R3 comprises a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring or a heteropolycyclic ring.

In an advantageous variation of the invention, R3 comprises



In a variation of the invention, R3 comprises $-CH_2-Z$.

Z comprises H, halogen, N_3, NCS, Ph, CN, NO_2, NX_1X_2, OX_3, OAc, O-acyl, O-aroyl, $O(CH_2)_dOH$, $O(CH_2)_dNX_1X_2$, NH-acyl, NH-aroyl, CHO, CF_3, $COOX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, alkyl, alcohol, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl or alkylsulfonyl.

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally a second heteroatom selected from O, N or S, or

X_1 and X2 together comprise part of an imide ring having about 5 to about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl or alkyl-NX_1X_2.

d is an integer from 0 to about 6.

In a variation of the invention, R3 comprises $-CH_2OH$ or $-CH_2Oalkyl$.

In a variation of the invention, R3 comprises $-CH_2-Z$.

Z comprises a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring or a

heterotricyclic ring; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the -$(CH_2)_n$- group and the Z group can be any available ring carbon atom or any available ring nitrogen atom.

In a variation of the invention, R3 comprises –CH_2–Z.

Z comprises 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidinyl, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the -$(CH_2)_n$- group and the Z group can be any available ring carbon atom or any available ring nitrogen atom.

In a variation of the invention R3 comprises –CH_2–Q–$(CH_2)_n$–Z.

Q comprises N, O, S, CH_3, SO_2 or OSO_2.

n is an integer from 0 to about 7.

Z comprises H, halogen, N_3, NCS, Ph, CN, NO_2, NX_1X_2, OX_3, OAc, O-acyl, O-aroyl, NH-acyl, NH-aroyl, $O(CH_2)_dOH$, $O(CH_2)_dNX_1X_2$, CHO, CF_3, $COOX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, alkyl, alcohol, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl or alkylsulfonyl.

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally a second heteroatom selected from O, N or S, or

X_1 and X2 together comprise part of an imide ring having about 5 to about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2.

d is an integer from 0 to about 6.

In a variation of the invention R3 comprises $-CH_2-Q-(CH_2)_n-Z$.

Q comprises N, O, S, CH_3, SO_2 or OSO_2.

n is an integer from 0 to about 7.

Z comprises a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom.

In a variation of the invention R3 comprises $-CH_2-Q-(CH_2)_n-Z$.

Q comprises N, O, S, CH_3, SO_2 or OSO_2.

n is an integer from 0 to about 7.

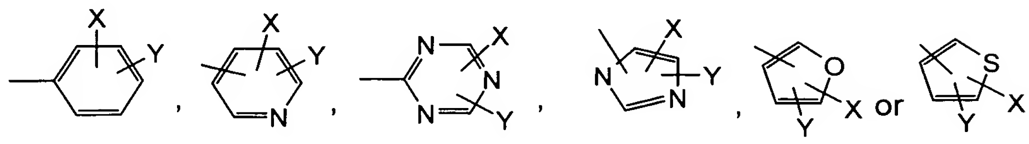
Z comprises 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidinyl, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom.

In a variation of the invention, R3 comprises $-CH_2-Q-(CH_2)_n-Z$.

Q comprises N, O, S, CH_3, SO_2 or OSO_2.

n is an integer from 0 to about 7.

Z comprises



wherein X and Y each independently comprise H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, O-acyl, O-aroyl, NH-acyl, NH-aroyl, CHO, CF_3, alcohol, $COOX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl, alkylsulfonyl or (when Z comprises a structure having two adjacent carbon atoms) methylene dioxy.

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally a second heteroatom selected from O, N or S, or

X_1 and X2 together comprise part of an imide ring having about 5 to about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl or alkyl-NX_1X_2.

In any variation of R3 when A is not a direct bond and B is N then R3 cannot be H or a C1-C3 alkyl.

R4 comprises $-(CH_2)_n-Z$.

n comprises an integer from 0 to about 7.

Z comprises H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, O-acyl, O-aroyl, NH-acyl, NH-aroyl, $O(CH_2)_dOH$, $O(CH_2)_dNX_1X_2$, CHO, CF_3, $COOX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, alkoxy, alkylmercapto, alkylamino, di-alkylamino alkylsulfinyl or alkylsulfonyl.

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally a second heteroatom selected from O, N or S, or

X_1 and X2 together comprise part of an imide ring having about 5 to about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl or alkyl-NX_1X_2.

d is an integer from 0 to about 6.

In a variation of the invention, R4 comprises $-(CH_2)_n-Z$.

n comprises an integer from 0 to about 7.

Z comprises a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members, a bicyclic ring, a heterobicyclic ring, a polycyclic ring, a heteropolycyclic ring; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom.

In a variation of the invention, R4 comprises $-(CH_2)_n-Z$.

n comprises an integer from 0 to about 7.

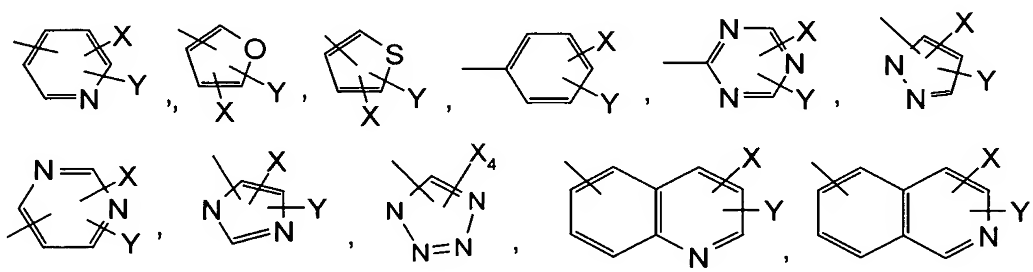
Z comprises 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidinyl, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group;

and wherein the connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom.

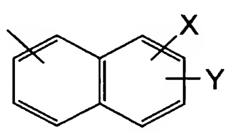
In an advantageous variation of the invention, R4 comprises $-(CH_2)_n-Z$.

n comprises an integer from 0 to about 7.

Z comprises



or



wherein X and Y each independently comprise H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, O-acyl, O-aroyl, NH-acyl, NH-aroyl, alcohol, CHO, CF_3, $COOX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl, alkylsulfonyl or (when Z comprises a structure having two adjacent carbon atoms) methylene dioxy.

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally a second heteroatom selected from O, N or S, or

X_1 and X2 together comprise part of an imide ring having about 5 to about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl or alkyl-NX_1X_2,

X_4 comprises H or alkyl.

In a variation of the invention, R4 comprises $-(CH_2)_n-Z$.

n comprises an integer from 0 to about 7.

Z comprises an unsaturated ring having 5 ring atoms and 0 to 4 independently selected heteroatoms as ring members fused to an unsaturated ring having 5 ring atoms and 0 to 4 independently selected heteroatoms as ring members, an unsaturated ring having 5 ring atoms and 0 to 4 independently selected heteroatoms as ring members fused to an unsaturated ring having 6 or 7 ring atoms and 0 to 5 independently selected heteroatoms as ring members or an unsaturated ring having 6 ring atoms and 0 to 5 independently selected heteroatoms as ring members fused to an unsaturated ring having 6 or 7 ring atoms and 0 to 5 independently selected heteroatoms as ring members.

In a variation of the invention, R4 comprises $-CH_2-Q-(CH_2)_n-Z$.

Q comprises N, O, S, CH_3, SO_2 or OSO_2.

n is an integer from 0 to about 7.

Z comprises H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, O-acyl, O-aroyl, $O(CH_2)_dOH$, $O(CH_2)_dNX_1X_2$, NH-acyl, NH-aroyl, CHO, CF_3, $COOX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, alkoxy, alkylmercapto, alkylamino or di-alkylamino.

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally a second heteroatom selected from O, N or S, or

X_1 and X2 together comprise part of an imide ring having about 5 to about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2.

d is an integer from 0 to about 6.

In a variation of the invention, R4 comprises $-CH_2-Q-(CH_2)_n-Z$.

Q comprises N, O, S, CH_3, SO_2 or OSO_2.

n is an integer from 0 to about 7.

Z comprises a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring or a heteropolycyclic ring.

In a variation of the invention, R4 comprises $-CH_2-Q-(CH_2)_n-Z$.

Q comprises N, O, S, CH_3, SO_2 or OSO_2.

n is an integer from 0 to about 7.

Z comprises a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom.

In a variation of the invention, R4 comprises $-CH_2-Q-(CH_2)_n-Z$.

Q comprises N, O, S, CH_3, SO_2 or OSO_2.

n is an integer from 0 to about 7.

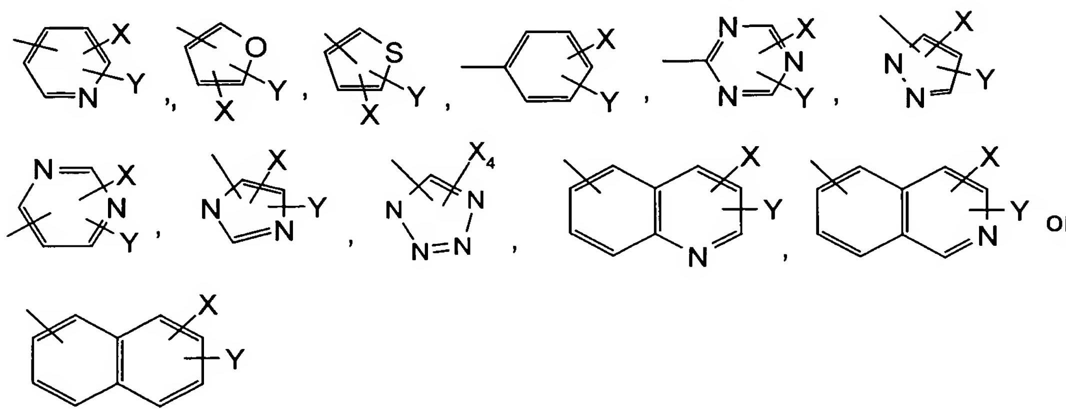
Z comprises 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidinyl, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom.

In a variation of the invention R4 comprises $-CH_2-Q-(CH_2)_n-Z$.

Q comprises N, O, S, CH_3, SO_2 or OSO_2.

n is an integer from 0 to about 7.

Z comprises



wherein X and Y each independently comprise H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, O-acyl, O-aroyl, NH-acyl, NH-aroyl, alcohol, CHO, CF_3, alcohol, $COOX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl, alkylsulfonyl or (when Z comprises a structure having two adjacent carbon atoms) methylene dioxy and X_4 comprises H or alkyl.

In a variation of the invention, R4 comprises $-(CH_2)_n-Q-(CH_2)_n-Z$.

Q comprises N, O, S, CH_3, SO_2 or OSO_2.

each n independently comprises an integer from 0 to about 7.

Z comprises an unsaturated ring having 5 ring atoms and 0 to 4 independently selected heteroatoms as ring members fused to an unsaturated ring having 5 ring atoms and 0 to 4 independently selected heteroatoms as ring members, an unsaturated ring having 5 ring atoms and 0 to 4 independently selected heteroatoms as ring members fused to an unsaturated ring having 6 or 7 ring atoms and 0 to 5 independently selected heteroatoms as ring members or an unsaturated ring having 6 ring atoms and 0 to 5 independently selected heteroatoms as ring members

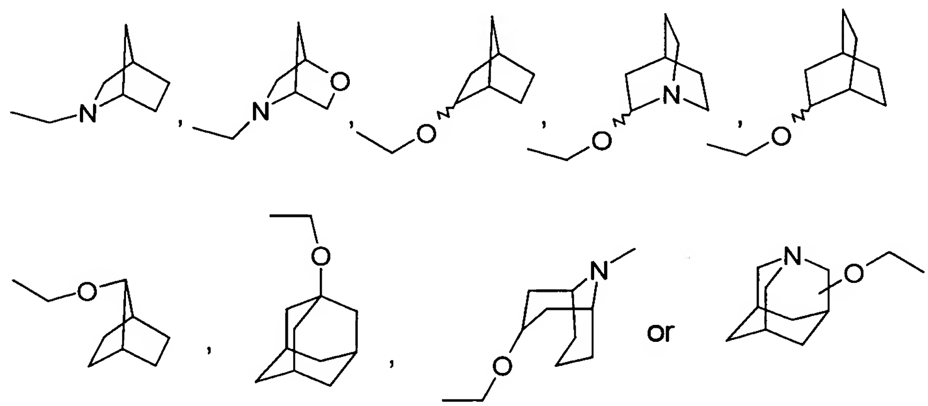
fused to an unsaturated ring having 6 or 7 ring atoms and 0 to 5 independently selected heteroatoms as ring members.

In a variation of the invention, R4 comprises $-CH_2-Q-(CH_2)_n-Z$.

Q comprises N, O, S, CH_3, SO_2 or OSO_2.

n is an integer from 0 to about 7.

Z comprises



In a variation of the invention R4 comprises $-T-(CH_2)_n-Z$.

n comprises an integer from 0 to about 7.

T comprises a carbocyclic ring having 3 to about 8 ring members, an unsaturated ring having 3 to about 8 carbon atoms as ring members, a heterocyclic ring having 3 to about 8 ring members, a heteroaromatic ring having 5 to about 8 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring or a heteropolycyclic ring.

Z comprises H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, O-acyl, O-aroyl, $O(CH_2)_dOH$, $O(CH_2)_dNX_1X_2$, NH-acyl, NH-aroyl, CHO, CF_3, $COOX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, alkoxy, alkylmercapto, alkylamino, di-alkylamino alkylsulfinyl or alkylsulfonyl.

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally a second heteroatom selected from O, N or S, or

X_1 and X2 together comprise part of an imide ring having about 5 to about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl or alkyl-NX_1X_2.

d is an integer from 0 to about 6.

In a variation of the invention R4 comprises $-T-(CH_2)_n-Z$.

n comprises an integer from 0 to about 7.

T comprises a carbocyclic ring having 3 to about 8 ring members, an unsaturated ring having 3 to about 8 carbon atoms as ring members, a heterocyclic ring having 3 to about 8 ring members, a heteroaromatic ring having 5 to about 8 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring or a heteropolycyclic ring.

Z comprises a carbocyclic ring having about 4 to about 7 ring members, a heterocyclic ring having about 4 to about 7 ring members, an aromatic ring having about 5 to about 7 ring members, a heteroaromatic ring having about 5 to about 7 ring members, a bicyclic ring, a heterobicyclic ring, a polycyclic ring, a heteropolycyclic ring; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the $-(CH_2)_n-$ group and the Z group can be any available ring carbon atom or any available ring nitrogen atom.

In a variation of the invention R4 comprises $-T-(CH_2)_n-Z$.

n comprises an integer from 0 to about 7.

T comprises a carbocyclic ring having 3 to about 8 ring members, an unsaturated ring having 3 to about 8 carbon atoms as ring members, a

heterocyclic ring having 3 to about 8 ring members, a heteroaromatic ring having 5 to about 8 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring or a heteropolycyclic ring.

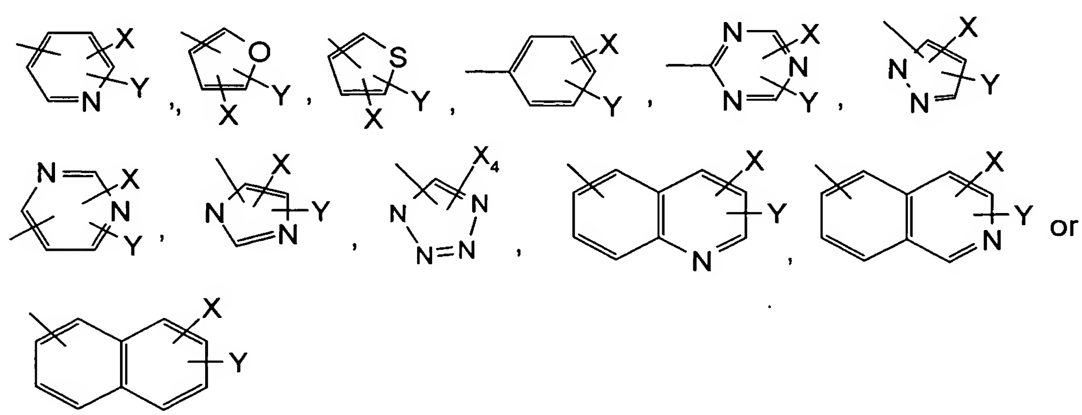
Z comprises 1-, 2- or 3-pyrrolidinyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, 2-, 3- or 4-thiomorpholinyl, 1-, 2- or 3-azetidinyl, 1- or 2-piperazinyl, 2- or 3-tetrahydrofuranyl; or any above group substituted on at least one available ring atom by an alkyl group; or any above group substituted on at least one available ring nitrogen atom by a benzyl group, a substituted benzyl group, an alkoxybenzyl group, a substituted alkoxybenzyl group, a benzhydryl group or a substituted benzhydryl group; and wherein the connecting point between the -$(CH_2)_n$- group and the Z group can be any available ring carbon atom or any available ring nitrogen atom.

In a variation of the invention R4 comprises –T–$(CH_2)_n$–Z.

n comprises an integer from 0 to about 7.

T comprises a carbocyclic ring having 3 to about 8 ring members, an unsaturated ring having 3 to about 8 carbon atoms as ring members, a heterocyclic ring having 3 to about 8 ring members, a heteroaromatic ring having 5 to about 8 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring or a heteropolycyclic ring.

Z comprises



wherein X and Y each independently comprise H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, O-acyl, O-aroyl, NH-acyl, NH-aroyl, alcohol, CHO, CF_3, $COOX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl, alkylsulfonyl or (when Z comprises a structure having two adjacent carbon atoms) methylene dioxy.

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally a second heteroatom selected from O, N or S, or

X_1 and X2 together comprise part of an imide ring having about 5 to about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl or alkyl-NX_1X_2,

X_4 comprises H or alkyl.

In a variation of the invention R4 comprises $-T-(CH_2)_n-Z$.

n comprises an integer from 0 to about 7.

T comprises a carbocyclic ring having 3 to about 8 ring members, an unsaturated ring having 3 to about 8 carbon atoms as ring members, a heterocyclic ring having 3 to about 8 ring members, a heteroaromatic ring having 5 to about 8 ring members, a bicyclic ring, a heterobicyclic ring, a tricyclic ring, a heterotricyclic ring, a polycyclic ring or a heteropolycyclic ring.

Z comprises an unsaturated ring having 5 ring atoms and 0 to 2 independently selected heteroatoms as ring members fused to an unsaturated ring having 5 ring atoms and 0 to 4 independently selected heteroatoms as ring members, an unsaturated ring having 5 ring atoms and 0 to 4 independently selected heteroatoms as ring members fused to an unsaturated ring having 6 or 7 ring atoms and 0 to 5 independently selected heteroatoms as ring members or an unsaturated ring having 6 ring atoms and 0 to 5 independently selected heteroatoms as ring members

fused to an unsaturated ring having 6 or 7 ring atoms and 0 to 5 independently selected heteroatoms as ring members.

In another variation of the invention R4 comprises $-Ph-(CH_2)_n-Z$.

n comprises an integer from 0 to about 7.

Z comprises H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, O-acyl, O-aroyl, $O(CH_2)_dOH$, $O(CH_2)_dNX_1X_2$, NH-acyl, NH-aroyl, CHO, CF_3, $COOX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, alkoxy, alkylmercapto, alkylamino or di-alkylamino.

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally heteroatom selected from O, N or S, or

X_1 and X2 together comprise part of an imide ring having about 5 to about 6 members.

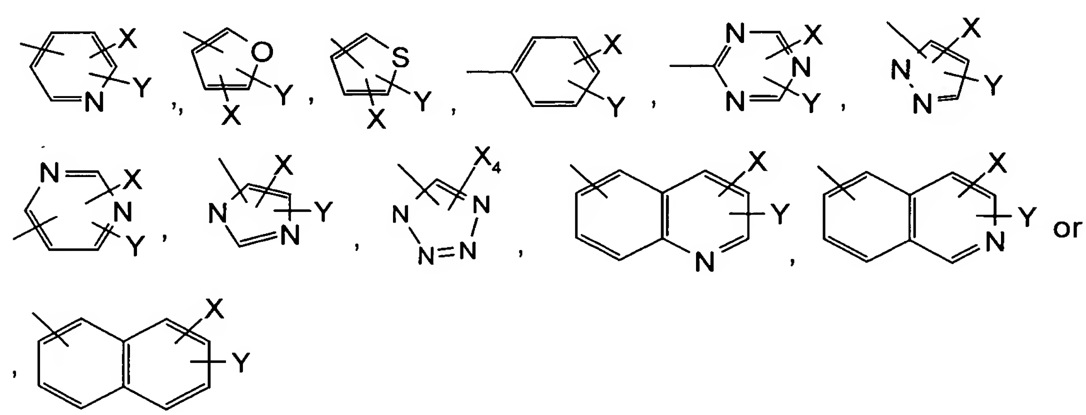
X_3 comprises H, alkyl, hydroxyloweralkyl or alkyl-NX_1X_2.

d is an integer from 0 to about 6.

In a variation of the invention, R4 comprises $-Ph-(CH_2)_n-Z$.

n comprises an integer from 0 to about 7.

Z comprises



wherein X and Y each independently comprise H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, O-acyl, O-aroyl, NH-acyl, NH-

aroyl, CHO, CF_3, alcohol, $COOX_3$, SO_3H, $SO_2NX_1X_2$, $CONX_1X_2$, alkoxy, alkylmercapto, alkylamino, di-alkylamino, alkylsulfinyl, lower-alkylsulfonyl or (when Z comprises a structure having two adjacent carbon atoms) methylene dioxy.

X_1 and X_2 each independently comprise H or alkyl, or

X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally a second heteroatom selected from O, N or S, or

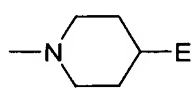
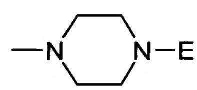
X_1 and X2 together comprise part of an imide ring having about 5 to about 6 members.

X_3 comprises H, alkyl, hydroxyloweralkyl or alkyl-NX_1X_2.

X_4 comprises H or alkyl.

In a variation of the invention R4 comprises $-Ph-(CH_2)_n-Z$.

n comprises an integer from 0 to about 7.

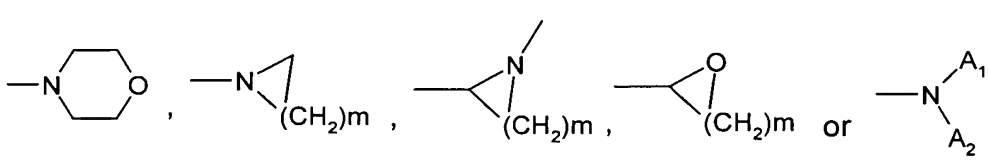
Z comprises  or .

E comprises a C1 to about C4, linear or branched alkyl group, a phenyl group, a substituted phenyl group, a benzyl group or a substituted benzyl group.

In a variation of the invention R4 comprises $-Ph-(CH_2)_n-Z$.

n comprises an integer from 0 to about 7.

Z comprises



m is an integer from 1 to about 5. A_1 and A_2 each independently comprise a C1 to about C4 alkyl group, a phenyl group or a substituted phenyl group.

In any of the above R4 variations when A is a direct bond and B is N and R5 is hydrogen and R2 has a nitrogen directly connected to the nitrogen of the amide at the 3-position of pyrazole ring, then R4 can not be a phenyl ring or a phenyl ring having one to three substitutions selected from halogen, trifluoromethyl, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, lower-alkyl substituted 1-pyrrolidinyl, lower-alkyl substituted 1-piperidinyl, lower-alkyl substituted 4-morpholinyl, and lower-alkyl substituted 1-piperazinyl.

R5 is present only when B is N and if present comprises H, alkyl or substituted alkyl.

It should be understood that:

when A is a direct bond and B is N then R1 cannot be H;

when A is not a direct bond and B is N then R3 cannot be H or a C1-C3 alkyl;

when A is a direct bond and B is N and R1 is a 6 member aromatic ring having 0 to 3 substituents independently selected from halogen, fluoromethyl and trifluoromethyl then R4 cannot be a 6 member aromatic ring having 0 to 3 substituents independently selected from halogen, fluoromethyl and trifluoromethyl;

when A is a direct bond and B is N and R5 is hydrogen and R2 has a nitrogen directly connected to the nitrogen of the amide at the 3-position of pyrazole ring, then R4 can not be a phenyl ring or a phenyl ring having one to three substitutions selected from halogen, trifluoromethyl, 1-pyrrolidinyl, 1-piperidinyl, 4-morpholinyl, 1-piperazinyl, lower-alkyl substituted 1-pyrrolidinyl, lower-alkyl substituted 1-piperidinyl, lower-alkyl substituted 4-morpholinyl, and lower-alkyl substituted 1-piperazinyl.

The inventive compounds include any and all isomers and steroisomers. In general, the compositions of the invention may be alternately formulated to comprise, consist of, or consist essentially of, any appropriate components herein disclosed. The compositions of the invention may additionally, or alternatively, be formulated so as to be devoid, or substantially free, of any components, materials, ingredients, adjuvants or species used in the prior art compositions or that are otherwise not necessary to the achievement of the function and/or objectives of the present invention.

Unless otherwise specifically defined, “acyl” refers to the general formula –C(O)alkyl.

Unless otherwise specifically defined, “acyloxy” refers to the general formula –O–acyl.

Unless otherwise specifically defined, “alcohol” refers to the general formula alkyl–OH and includes primary, secondary and tertiary variations.

Unless otherwise specifically defined, “alkyl” or “lower alkyl” refers to a linear, branched or cyclic alkyl group having from 1 to about 16 carbon atoms including, for example, methyl, ethyl, propyl, butyl, hexyl, octyl, isopropyl, isobutyl, tert-butyl, cyclopropyl, cyclohexyl, cyclooctyl, vinyl and allyl. The alkyl group can be saturated or unsaturated. The alkyl group can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position. Unless otherwise specifically limited, a cyclic alkyl group includes monocyclic, bicyclic, tricyclic, tetracyclic and polycyclic rings, for example norbornyl, adamantyl and related terpenes.

Unless otherwise specifically defined, “alkoxy” refers to the general formula –O–alkyl.

Unless otherwise specifically defined, “alkylmercapto” refers to the general formula –S–alkyl.

Unless otherwise specifically defined, “alkylamino” refers to the general formula –(NH)–alkyl.

Unless otherwise specifically defined, “di-alkylamino” refers to the general formula –N–(alkyl)$_2$. Unless otherwise specifically limited di-alkylamino includes cyclic amine compounds such as piperidine and morpholine.

Unless otherwise specifically defined, an aromatic ring is an unsaturated ring structure having about 5 to about 7 ring members and including only carbon as ring atoms. The aromatic ring structure can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position.

Unless otherwise specifically defined, "aryl" refers to an aromatic ring system that includes only carbon as ring atoms, for example phenyl, biphenyl or naphthyl. The aryl group can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position.

Unless otherwise specifically defined, "aroyl" refers to the general formula –C(=O)–aryl.

Unless otherwise specifically defined, a bicyclic ring structure comprises 2 fused rings that include only carbon as ring atoms. The bicyclic ring structure can be saturated or unsaturated. The bicyclic ring structure can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position. The individual rings may or may not be of the same type. Examples of bicyclic ring structures include naphthalene and bicyclooctane.

Unless otherwise specifically defined, a carbocyclic ring is a non-aromatic ring structure, saturated or unsaturated, having about 3 to about 8 ring members that includes only carbon as ring atoms, for example, benzene or cyclohexane. The carbocyclic ring can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position.

Unless otherwise specifically defined, "halogen" refers to an atom selected from fluorine, chlorine, bromine and iodine.

Unless otherwise specifically defined, a heteroaromatic ring is an unsaturated ring structure having about 5 to about 8 ring members independently selected from carbon atoms and one or more heteroatoms, including oxygen, nitrogen and/or sulfur, for example, pyridine, furan, quinoline, and their derivatives. The heteroaromatic ring can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position.

Unless otherwise specifically defined, a heterobicyclic ring structure comprises 2 fused rings having ring members independently selected from carbon and one or more heteroatoms, including oxygen, nitrogen and/or sulfur. The

heterobicyclic ring structure is typically unsaturated. The heterobicyclic ring can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position. The individual rings may or may not be of the same type. Examples of heterobicyclic ring structures include isobenzofuran and indole.

Unless otherwise specifically defined, a heterocyclic ring is a saturated ring structure having about 3 to about 8 ring members independently selected from carbon atoms and one or more heteroatoms, including oxygen, nitrogen and/or sulfur; for example, piperidine, morpholine, piperazine, pyrrolidine, thiomorpholine, and their derivatives. The heterocyclic ring can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position.

Unless otherwise specifically defined, a heterotricyclic ring structure comprises 3 fused rings having ring members independently selected from carbon and one or more heteroatoms, including oxygen, nitrogen and/or sulfur. The heterotricyclic ring structure is typically unsaturated. The heterotricyclic ring structure can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position. The individual rings may or may not be of the same type. Examples of heterotricyclic ring structures include carbazole, phenanthroline and phenazine.

Unless otherwise specifically defined, a heteropolycyclic ring structure comprises more than 3 fused rings having ring members independently selected from carbon and one or more heteroatoms, including oxygen, nitrogen and/or sulfur. The heteropolycyclic ring structure is typically unsaturated. The heteropolycyclic ring structure can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position. The individual rings may or may not be of the same type. Examples of heteropolycyclic ring structures include azaadamantine, tropane and homotropane.

Unless otherwise specifically defined, the term "phenacyl" refers to the general formula –phenyl–acyl.

Unless otherwise specifically defined, a polycyclic ring structure comprises more than 3 fused rings and includes carbon as ring atoms. The polycyclic ring

structure can be saturated or unsaturated. The polycyclic ring structure can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position. The individual rings may or may not be of the same type. Examples of polycyclic ring structures include adamantine, bicyclooctane, norbornane and bicyclononanes.

Unless otherwise specifically defined, a spirocycle refers to a ring system wherein a single atom is the only common member of two rings. A spirocycle can comprise a saturated carbocyclic ring comprising about 3 to about 8 ring members, a heterocyclic ring comprising about 3 to about 8 ring atoms wherein up to about 3 ring atoms may be N, S, or O or a combination thereof.

Unless otherwise specifically defined, a tricyclic ring structure comprises 3 fused rings and includes carbon as ring atoms. The tricyclic ring structure can be saturated or unsaturated. The tricyclic ring structure can be unsubstituted, singly substituted or, if possible, multiply substituted, with substituent groups in any possible position. and may be substituted or unsubstituted. The individual rings may or may not be of the same type. Examples of tricyclic ring structures include fluorene and anthracene.

Substituent groups for the above moieties useful in the invention are those groups that do not significantly diminish the biological activity of the inventive compound. Substituent groups that do not significantly diminish the biological activity of the inventive compound include, for example, H, halogen, N_3, NCS, CN, NO_2, NX_1X_2, OX_3, OAc, O-acyl, O-aroyl, NH-acyl, NH-aroyl, NHCOalkyl, CHO, CF_3, $COOX_3$, SO_3H, PO_3H_2, $SO_2NX_1X_2$, $CONX_1X_2$, alkyl, alcohol, alkoxy, alkylmercapto, alkylamino, di-alkylamino, sulfonamide, thioalkoxy or methylene dioxy when the substituted structure has two adjacent carbon atoms, wherein X_1 and X_2 each independently comprise H or alkyl, or X_1 and X_2 together comprise part of a heterocyclic ring having about 4 to about 7 ring members and optionally one additional heteroatom selected from O, N or S, or X_1 and X2 together comprise part of an imide ring having about 5 to about 6 members and X_3 comprises H, alkyl, hydroxyloweralkyl, or alkyl-NX_1X_2. Unless otherwise specifically limited a substituent group may be in any possible position.

Some of the inventive compounds showed a high affinity for at least one of the cannabinoid receptors. Thus, an aspect of the invention is use of at least one

of the inventive compounds to interact with cannabinoid receptors.

Some of the novel pyrazole derivatives show selectivity for the CB1 cannabinoid receptor. These inventive CB1 selective analogs are able to interact with the CB1 receptor without affecting the peripheral (CB2) receptor to the same degree. Therefore, still another aspect of the invention is use of at least one of the inventive compounds to preferentially interact with the CB1 receptor.

Additionally, known cannabimimetic pyrazole ligands generally have long *in vivo* half-lives and are more lipophilic than desired for optimal *in vivo* activity. Some of the novel pyrazole analogs described herein are less lipophilic than known cannabimimetic pyrazole ligands and have shorter *in vivo* half-lives then known pyrazole analogs, providing the compounds of this embodiment with a favorable therapeutic profile. Therefore, yet another aspect of the invention is a cannabimimetic pyrazole analog that is less lipophilic than known cannabimimetic pyrazole analogs.

Some of the novel pyrazole analogs described herein are CB1 cannabinoid receptor antagonists that prevent binding of endogenous agonists to the cannabinoid receptors and thereby block the biological actions of such endogenous agonists. Therefore, a further aspect of the invention is use of at least one of the inventive compounds to prevent binding of a cannabinoid agonist to the CB1 cannabinoid receptor.

The inventive pyrazole analogs described herein, and physiologically acceptable salts thereof, have pharmacological properties when administered in therapeutically effective amounts for providing a physiological effect useful to treat marijuana abuse, obesity, schizophrenia, epilepsy, stress, memory disorders, migraine, vomiting, thymic disorders, dyskinesia, kinetic disorder, anxiety disorders, psychotic disorders, cognitive disorders, appetite disorders, mood disorders, delirious disorders, neuropathies, Parkinson's disease, Alzheimer's disease, depression, psychosomatic-induced disease, as well as for alcohol, opioid, nicotine and cocaine addiction, etc. Additionally, these analogs can be used in cancer chemotherapy. Thus, another aspect of the invention is the administration of a therapeutically effective amount of an inventive compound, or a physiologically acceptable salt thereof, to an individual or animal to provide a physiological effect.

A better understanding of the invention will be obtained from the following detailed description of the article and the desired features, properties, characteristics, and the relation of the elements as well as the process steps, one with respect to each of the others, as set forth and exemplified in the description and illustrative embodiments.

Brief Description of the Drawings

Figure 1 is a graph of a dose vs. response curve for inventive compound 1-5.

Description of Some Preferred Embodiments

As used herein a "therapeutically effective amount" of a compound, is the quantity of a compound which, when administered to an individual or animal, results in a sufficiently high level of that compound in the individual or animal to cause a physiological response. The inventive compounds described herein, and physiologically acceptable salts thereof, have pharmacological properties when administered in therapeutically effective amounts for providing a physiological response useful to treat marijuana abuse, obesity, schizophrenia, epilepsy, stress, memory disorders, migraine, vomiting, thymic disorders, dyskinesia, kinetic disorder, anxiety disorders, psychotic disorders, cognitive disorders, appetite disorders, mood disorders, delirious disorders, neuropathies, Parkinson's disease, Alzheimer's disease, depression, psychosomatic-induced disease, as well as for alcohol, opioid, nicotine and cocaine addiction, etc. Additionally, these analogs can be useful in cancer chemotherapy. Typically, a "therapeutically effective amount" of an inventive compound is believed to range from about 10 mg/day to about 1,000 mg/day.

As used herein, an "individual" refers to a human. An "animal" refers to, for example, veterinary animals, such as dogs, cats, horses and the like, and farm animals, such as cows, pigs and the like.

The compound of the present invention can be administered by a variety of known methods, including orally, rectally, or by parenteral routes (e.g., intramuscular, intravenous, subcutaneous, nasal or topical). The form in which the compounds are administered will be determined by the route of administration.

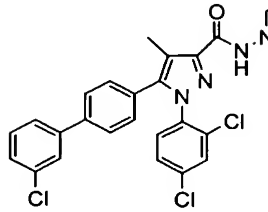
Such forms include, but are not limited to, capsular and tablet formulations (for oral and rectal administration), liquid formulations (for oral, intravenous, intramuscular, subcutaneous, ocular, intranasal, inhalation-based and transdermal administration) and slow releasing microcarriers (for rectal, intramuscular or intravenous administration). The formulations can also contain a physiologically acceptable vehicle and optional adjuvants, flavorings, colorants and preservatives. Suitable physiologically acceptable vehicles include, for example, saline, sterile water, Ringer's solution and isotonic sodium chloride solutions. The specific dosage level of active ingredient will depend upon a number of factors, including, for example, biological activity of the particular preparation, age, body weight, sex and general health of the individual being treated.

The following examples are given for purposes of illustration only in order that the present invention may be more fully understood. These examples are not intended to limit in any way the scope of the invention unless otherwise specifically indicated.

Examples:

A number of inventive cannabimimetic pyrazole derivatives were prepared. Table 1 illustrates some prepared CB1 selective pyrazole analogs (compounds 1-1 to 1-29).

Table 1



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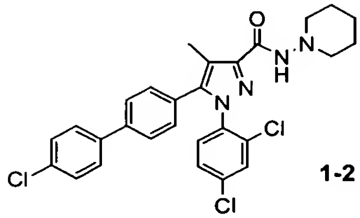

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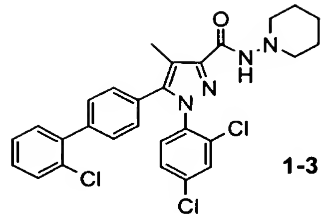

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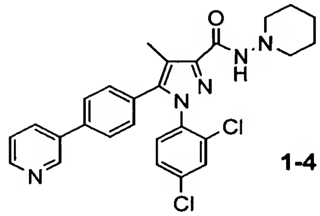
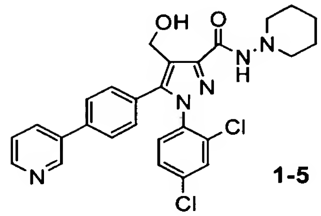


1-4



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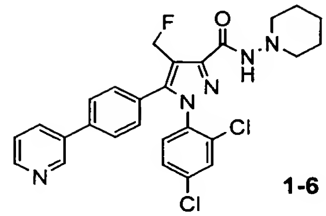

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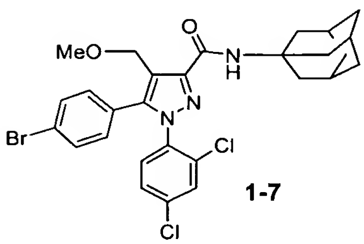

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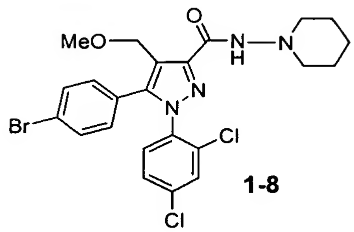

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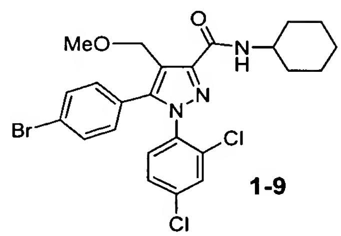

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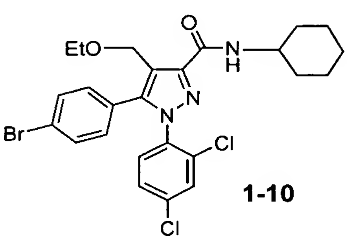

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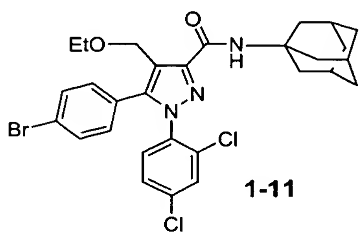

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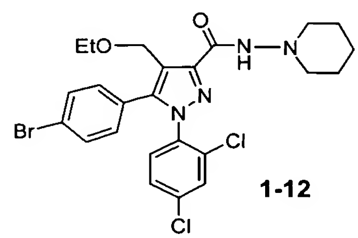

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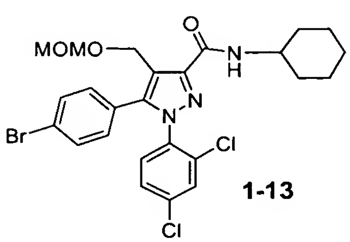

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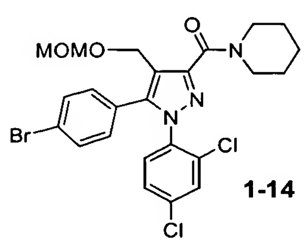

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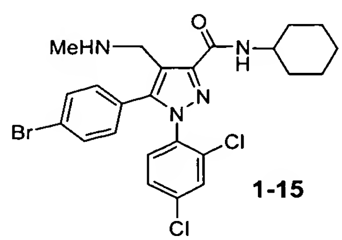

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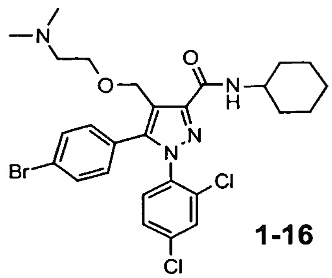

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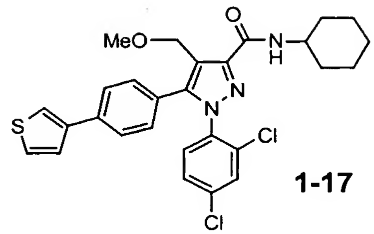

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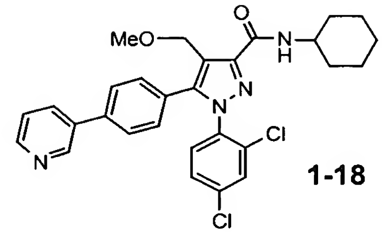
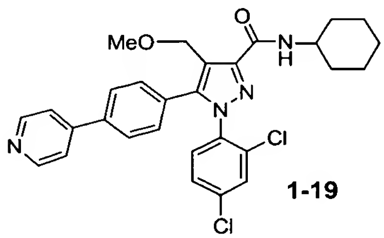


1-18



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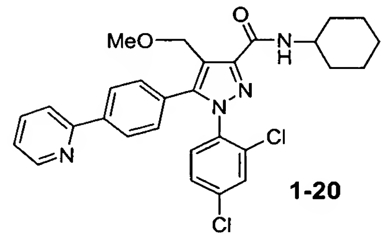

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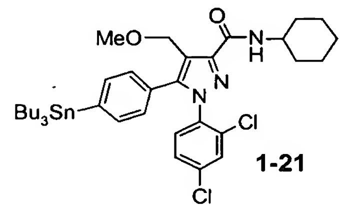

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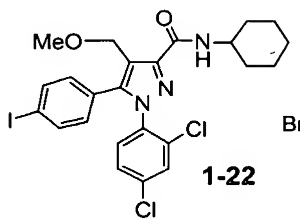

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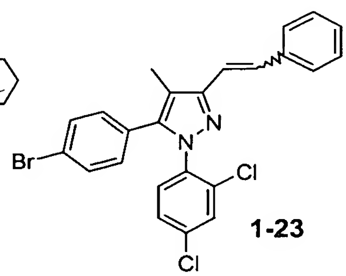

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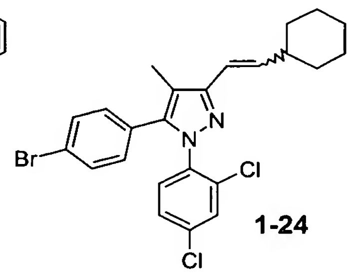

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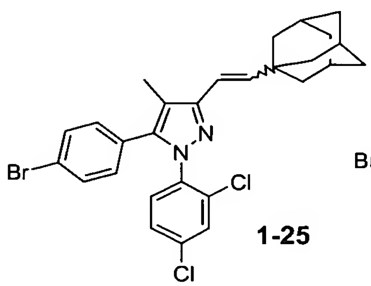

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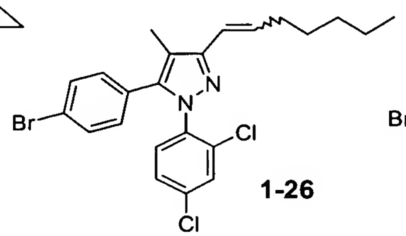

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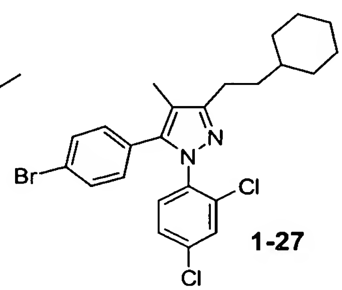

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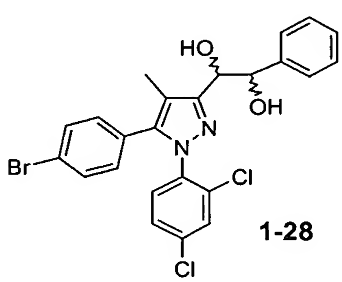

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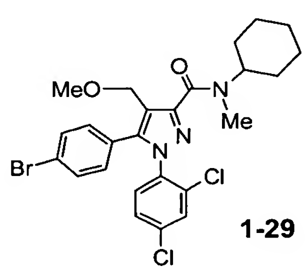
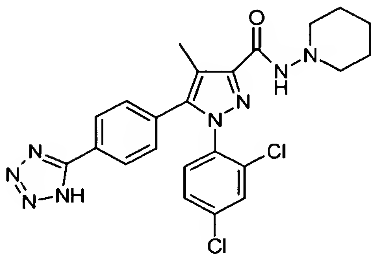


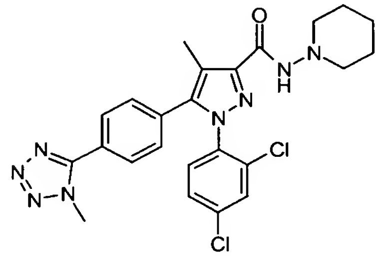
1-29

Table 2 illustrates some prepared CB1 selective pyrazole analogs (compounds 2-1 to 2-22)

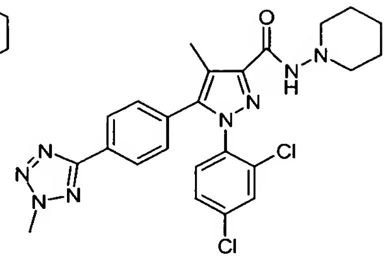
Table 2



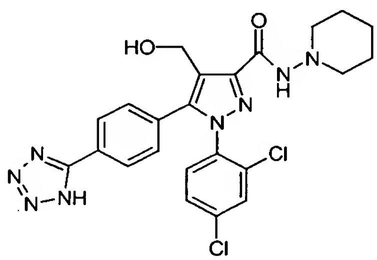
2-1



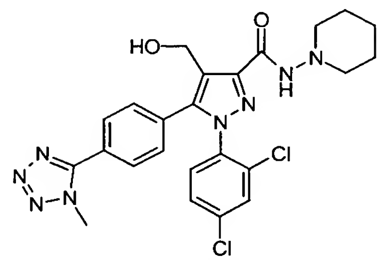
2-2



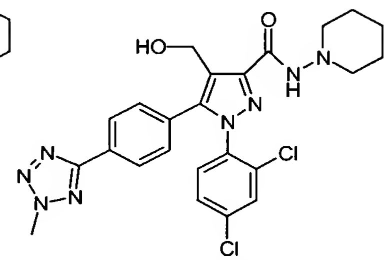
2-3



2-4



2-5



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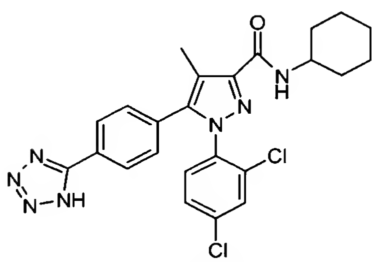

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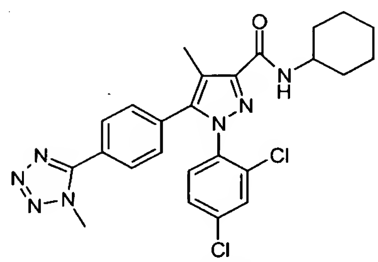

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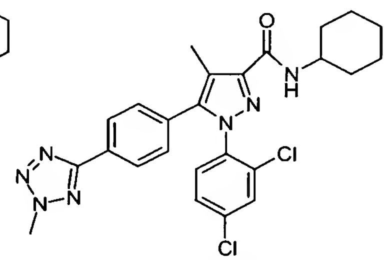
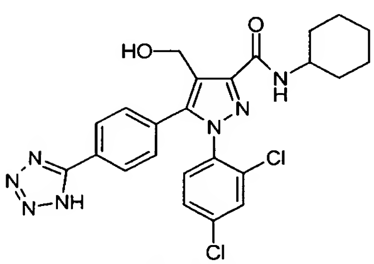
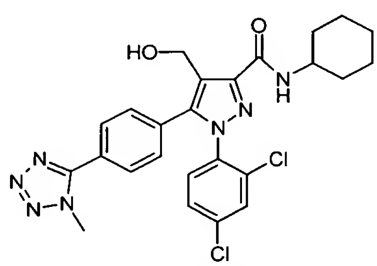


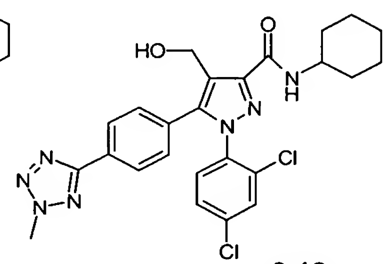
2-9



2-10

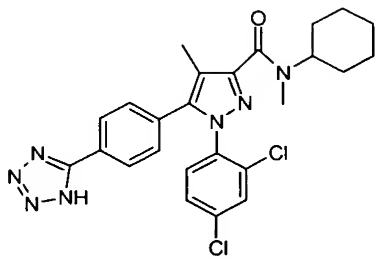


2-11

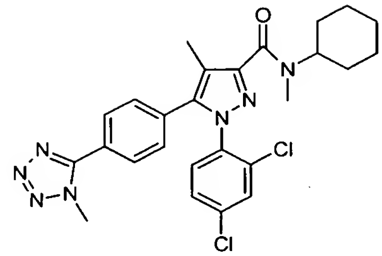


2-12

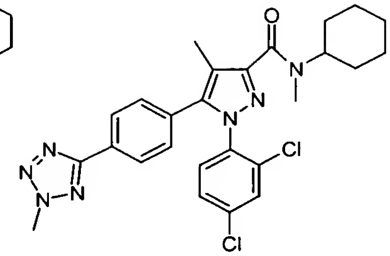
Table 2 (cont.)



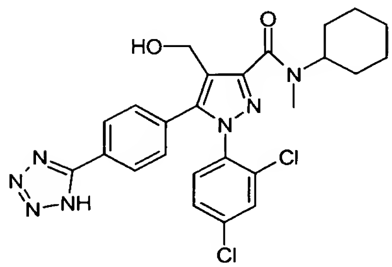
2-13



2-14



2-15



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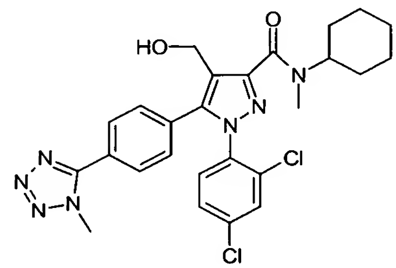

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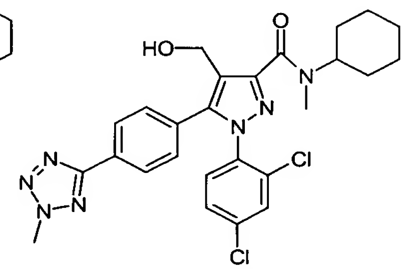

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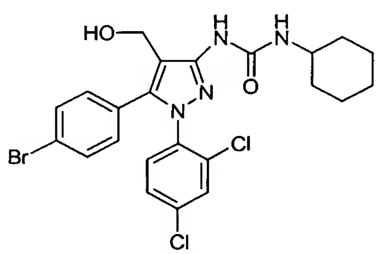

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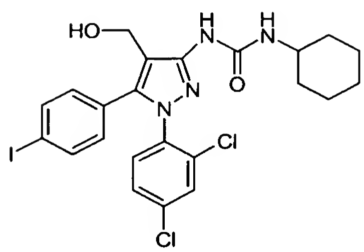

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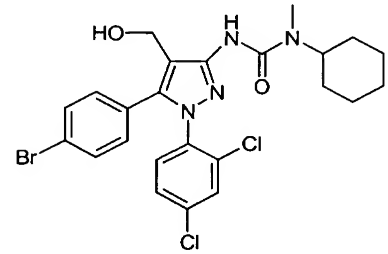

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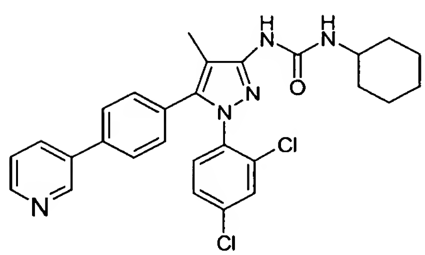
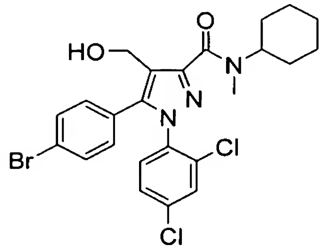


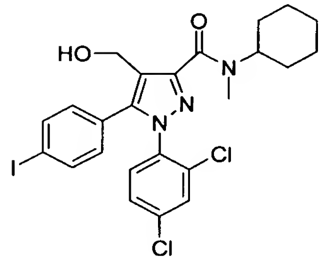
2-22

Table 3 illustrates some prepared pyrazole analogs (compounds 3-1 to 3-25).

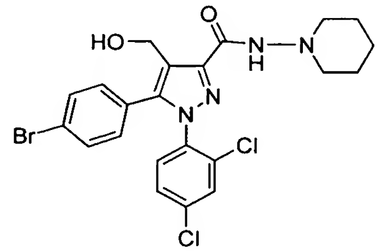
Table 3



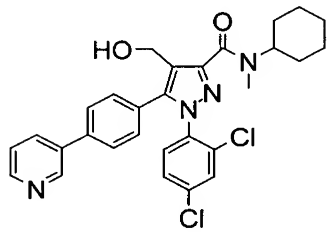
3-1



3-2



3-3



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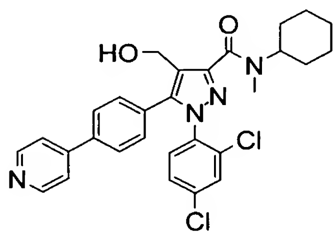

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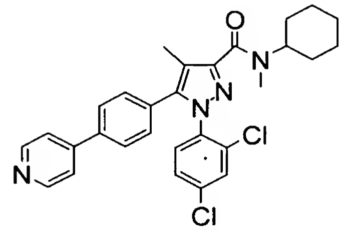

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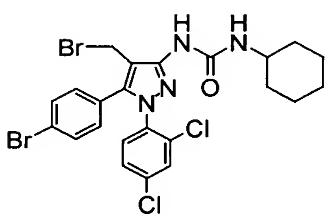
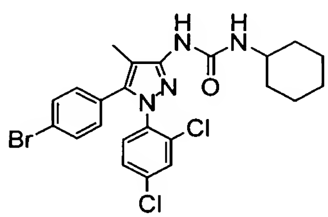


3-7



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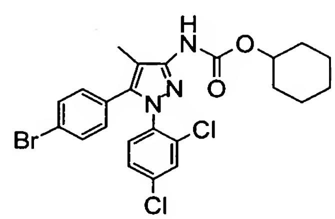
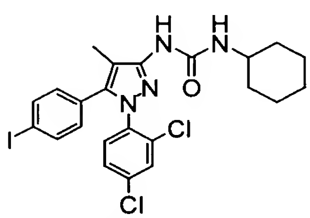
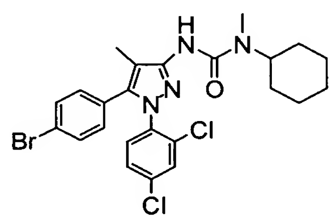


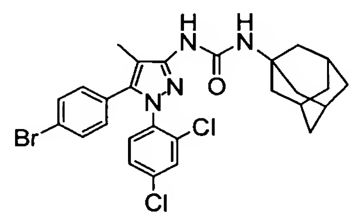
3-9



3-10



3-11



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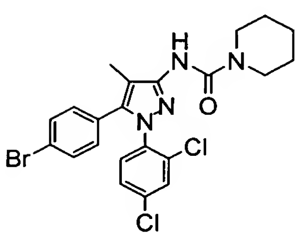

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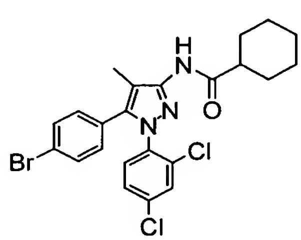
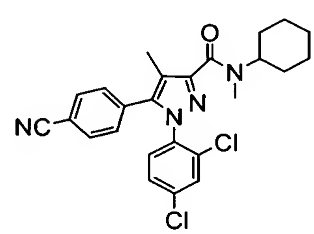
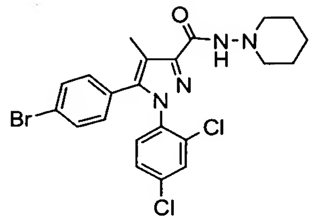


3-14



3-15

Table 3 (cont.)



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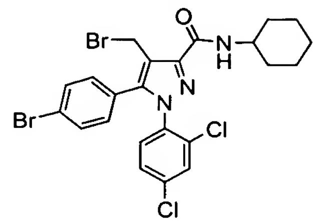

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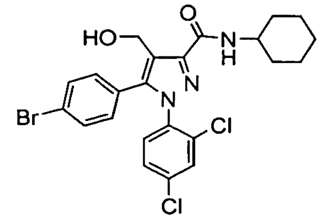
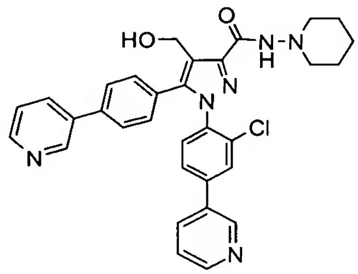
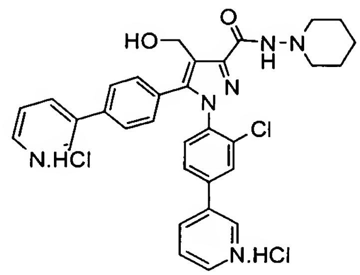


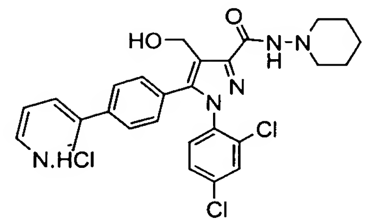
3-18



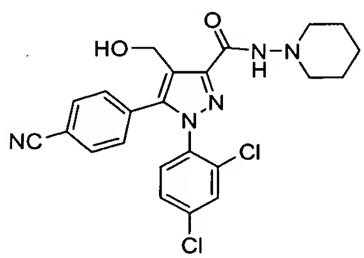
3-19



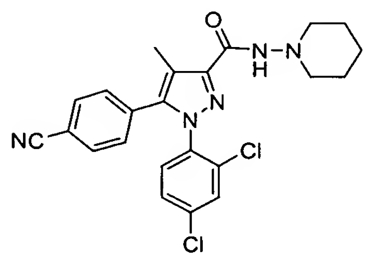
3-20



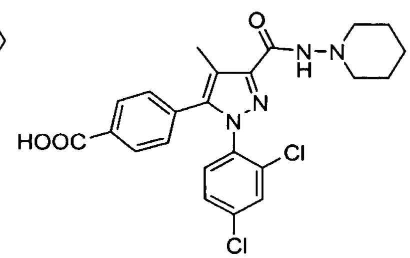
3-21



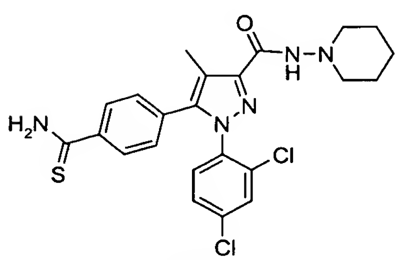
3-22



3-23



3-24



3-25

Some of the inventive analogs were tested for CB2 receptor binding affinity and for CB1 receptor affinity (to determine selectivity). As used herein, "binding affinity" is represented by the K_i value which is the inhibition constant correlated

with the concentration of an analog required to occupy the 50% of the total number (Bmax) of the receptors. The lower the K_i value the higher the binding affinity. As used herein an analog is said to have "binding selectivity" if it has higher binding affinity for one receptor compared to the other receptor; e.g. a cannabinoid analog which has a K_i of 0.1 nM for CB1 and 10 nM for CB2, is 100 times more selective for the CB1 receptor.

For the CB1 receptor binding studies, membranes were prepared from rat forebrain membranes according to the procedure of P.R. Dodd et al, A Rapid Method for Preparing Synaptosomes: Comparison with Alternative Procedures, Brain Res., 107 - 118 (1981). The binding of the novel analogues to the CB1 cannabinoid receptor was assessed as described in W.A. Devane et al, Determination and Characterization of a Cannabinoid Receptor in a Rat Brain, Mol. Pharmacol., 34, 605 - 613 (1988) and A. Charalambous et al, 5'-azido Δ^8 - THC: A Novel Photoaffinity Label for the Cannabinoid Receptor, J. Med. Chem., 35, 3076 - 3079 (1992) with the following changes. The above articles are incorporated by reference herein.

Membranes, previously frozen at -80°C, were thawed on ice. To the stirred suspension was added three volumes of TME (25 mM Tris-HCl buffer, 5 mM $MgCl_2$ and 1 mM EDTA) at a pH 7.4. The suspension was incubated at 4°C for 30 min. At the end of the incubation, the membranes were pelleted and washed three times with TME.

The treated membranes were subsequently used in the binding assay described below. Approximately 30 μg of membranes were incubated in silanized 96-well microtiter plate with TME containing 0.1% essentially fatty acid-free bovine serum albumin (BSA), 0.8 nM [^{3}H] CP-55,940, and various concentrations of test materials in a final volume of 200 μL. The assays were incubated for 1 hour at 30 °C and then immediately filtered using Packard Filtermate 196 harvester and Whatman GF/C filterplates and washed with wash buffer (TME) containing 0.5% BSA. Radioactivity was detected using MicroScint 20 scintillation cocktail added directly to the dried filterplates, and the filterplates were counted using a Packard Instruments Top-Count. Nonspecific binding was assessed using 100 nM CP-55,940. Data collected from three independent experiments performed with duplicate determinations was normalized between 100% and 0% specific binding

for [^{3}H] CP-55,940, determined using buffer and 100 nM CP-55,940. The normalized data was analyzed using a 4-parameter nonlinear logistic equation to yield IC_{50} values. Data from at least two independent experiments performed in duplicate was used to calculate IC_{50} values which were converted to K_i values using the assumptions of Cheng et al, Relationship Between the Inhibition Constant (K_i) and the concentration of Inhibitor which causes 50% Inhibition (IC_{50}) of an Enzymatic Reaction, Biochem. Pharmacol., 22, 3099-3102, (1973), which is incorporated by reference herein.

For the CB2 receptor binding studies, membranes were prepared from frozen mouse spleen essentially according to the procedure of P.R. Dodd et al, A Rapid Method for Preparing Synaptosomes: Comparison with Alternative Procedures, Brain Res., 226, 107 - 118 (1981) which is incorporated by reference herein. Silanized centrifuge tubes were used throughout to minimize receptor loss due to adsorption. The CB2 binding assay was conducted in the same manner as for the CB1 binding assay. The binding affinities (K_i) were also expressed in nanomoles (nM).

For the compounds of Table 1 the CB1 cannabinoid receptor binding affinities (Ki) for the synthesized analogs range between 1.51 and 85.1. The CB2 cannabinoid receptor binding affinities (Ki) for the synthesized analogs range between 5.81 and 2312. The CB1 cannabinoid receptor selectivity for some of the synthesized analogs range from about 2 to about 452. The CB2 cannabinoid receptor selectivity for some of the synthesized analogs range from about 1 to about 4. The results are summarized in Table 4.

Table 4

cmpnd no.	affinities		selectivity	
	CB1	CB2	CB1	CB2
1-1	1.5	741	491	
1-2	5.8	1595	274	
1-3	85.1	1370	16	
1-4	11.2	1326	118	
1-5	5.8	2312	398	
1-6	15.1	1927	128	

Table 4				
cmpnd no.	affinities		selectivity	
	CB1	CB2	CB1	CB2
1-7	53	1676	32	
1-8	19	561	31	
1-9	4	495	124	
1-10	54	842	16	
1-11	105	47460	452	
1-12	46	490	11	
1-13	15	54	3.6	
1-14	395	3102	7.8	
1-15	172	397	2.3	
1-16	24	140	5.8	
1-17	241	968	4.0	
1-18	62	646	10.4	
1-19	160	2980	18.6	
1-20	51	277	5.4	
1-21	2970	2744		1.1
1-22	15	675	45	
1-23	331	16420	49.6	
1-24	141	10570	75.0	
1-25	17680	4006		4.4
1-26	7677	52890	6.9	
1-27	1043	26390	25.3	
1-28	1067	3926	3.7	
1-29	273	2038	7.5	

For the compounds of Table 2 the CB1 cannabinoid receptor binding affinities (Ki) for the synthesized analogs range between 6 and 1844. The CB2 cannabinoid receptor binding affinities (Ki) for the synthesized analogs range between 36.5 and 13585. The CB1 cannabinoid receptor selectivity for some of the synthesized analogs range from about 1 to about 546. The CB2 cannabinoid

receptor selectivity for compound 2-14 was 1.4. The results are summarized in Table 5.

Table 5

cmpnd no.	affinities		selectivity	
	CB1	CB2	CB1	CB2
2-1	455	702	1.5	
2-2	90	242	2.7	
2-3	6	517	86.2	
2-4	1844	13585	7.4	
2-5	203	2128	10.5	
2-6	18	2170	120.5	
2-8	120	1069	8.9	
2-9	20	381	19	
2-10	192	463	2.4	
2-11	118	122	1	
2-12	37	36.5	1	
2-13	543	6361	117.8	
2-14	1271	941		1.4
2-15	105	551	5.2	
2-16	293	1119	3.8	
2-17	1082	1414	1.3	
2-18	210	641	3.0	
2-19	9	4920	546.7	
2-21	296	4473	15.1	
2-22	29	10863	374.6	

For the compounds of Table 3 the CB1 cannabinoid receptor binding affinities (Ki) for the synthesized analogs range between 6 and 4232. The CB2 cannabinoid receptor binding affinities (Ki) for the synthesized analogs range between 127 and 27054. The CB1 cannabinoid receptor selectivity for some of the synthesized analogs range from about 1.3 to about 838. The results are summarized in Table 6.

Table 6

	affinities		selectivity
cmpnd no.	CB1	CB2	CB1
3-1	29	1802	62.1
3-2	18	528	29.3
3-3	46	490	10.6
3-4	227	759	3.3
3-5	90	294	3.3
3-6	189	3289	17.4
3-7	38	136	3.6
3-8	6.8	4319	635.2
3-9	69	449	6.5
3-10	26	21791	838.1
3-11	29	917	31.6
3-12	259	756	2.9
3-13	47	284	6.0
3-14	4232	27054	6.4
3-15	50	10825	216.5
3-16	17	897	52.8
3-17	46	3475	75.5
3-18	6	2120	353.3
3-19	146	1921	13.2
3-20	154	1678	10.9
3-21	76	207	2.7
3-22	64	2737	42.8
3-23	22	4693	213.3
3-24	738	934	1.3
3-25	86	127	1.5

Preparation of compounds

General. Column chromatography was carried out by using active silica gel (230–400 mesh) available from Selecto Scientific of Suwanee, Georgia. Eluents were distilled before use. Solvents for reactions were dried or purified as required. Reactions were carried out under argon atmosphere unless otherwise noted. All of the reagents are available from Sigma-Aldrich Fine Chemicals of Milwaukee, Wisconsin and/or Lancaster Synthesis Inc. of Windham, New Hampshire.

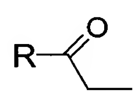
Modification of the direct aromatic substitution at pyrazole position 1 can be obtained by varying the respective starting hydrazine (i.e. 2,4-dichlorophenylhydrazine hydrochloride). Typically the starting hydrazine will having the general formula:

$$Ar{-}NHNH_2$$

Modification at pyrazole position 3 can be obtained by varying the respective starting material (i.e. 1-aminopiperidine). Typically the starting material will have the general formula:

$$RNH_2$$

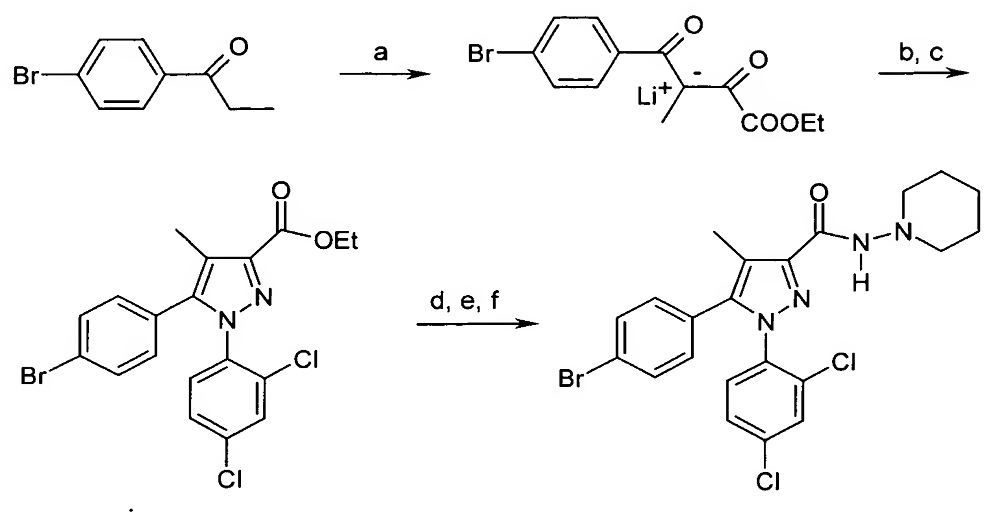
Most of the compounds with substitutions at pyrazole position 5 can be obtained through method A, disclosed below, by varying the starting material (4'-bromopropiophenone shown). Typically the starting material will have the general formula:



The synthesis of most of the above starting materials is disclosed in the existing literature. See, for example, Synthesis, 4, 1999, 588-592. Synthesis of the starting materials not disclosed in the existing literature can be performed by a person skilled in the art using analogous chemistries and with no more than routine experimentation.

General procedure for the preparation of intermediate (Int.) A and Int B:

Method A: Modification at Pyrazole Positions 1, 3 and 5



Int A **Int B**

(a) LiHMDS, ether, then EtO_2CCO_2Et; (b) 2, 4-Dichlorophenylhydrazine hydrochloride, EtOH; (c) AcOH; (d) KOH/MeOH, HCl/H_2O; (e) $SOCl_2$, toluene; (f) 1-Aminopiperidine, Et_3N, CH_2Cl_2.

Lithium salt of ethyl 2,4-dioxo-3-methyl-4-(4-bromophenyl)butanoate. To a magnetically stirred solution of lithium bis(trimethylsilyl)amide (40 mL, 1.0 M solution in hexane, 40 mmol) in diethyl ether (120 mL) was added a solution of 4'-bromopropiophenone (8.52 g, 40 mmol) in diethyl ether (50 mL) at –78 °C. After the mixture was stirred at the same temperature for an additional 45 min, diethyl oxalate (6.4 mL, 47 mmol) was added to the mixture. The reaction mixture was allowed to warm to room temperature (RT) and stirred for 16 h. The precipitate was filtered, washed with diethyl ether, and dried under vacuum to afford the lithium salt.

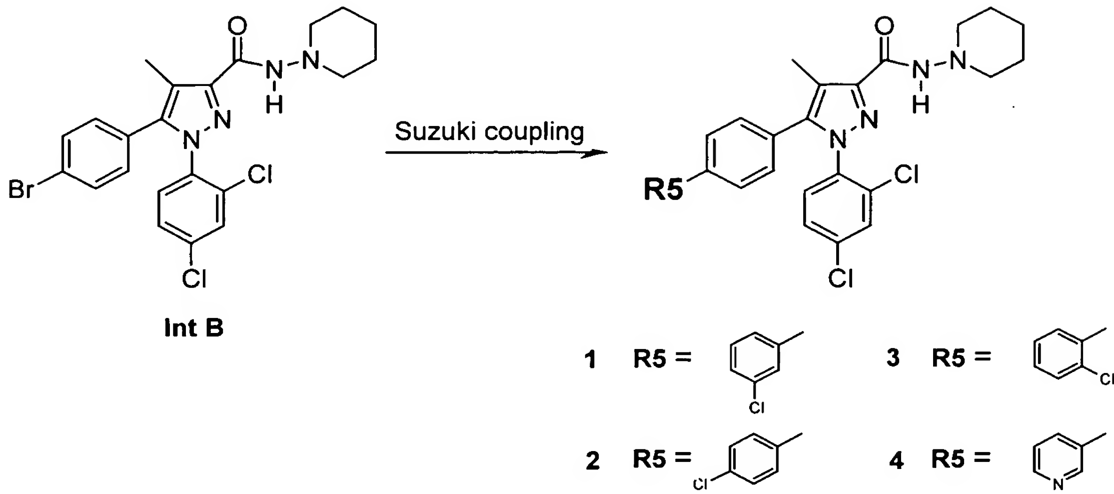
1-(2,4-Dichlorophenyl)-4-methyl-5-(4-bromophenyl)-1*H*-pyrazole-3-carboxylic acid, Ethyl Ester (Int. A). To a magnetically stirred solution of the above lithium salt (0.64g, 2.0 mmol) in 10 mL of ethanol was added 2,4-dichlorophenylhydrazine hydrochloride (0.47g, 2.2 mmol) at room temperature.

The resulting mixture was stirred at room temperature for 20 h. The precipitate was filtered, washed with ethanol and diethyl ether, and then dried under vacuum to give a light yellow solid. This solid was dissolved in acetic acid (7 mL) and heated under reflux for 24 h. The reaction mixture was poured into cold water and extracted multiple times with ethyl acetate. The combined extracts were washed with water, saturated aqueous sodium bicarbonate, and brine, dried over anhydrous sodium sulfate, filtered, and evaporated. Purification by flash column chromatography on silica gel gave the expected ester Int. A.

***N*-(Piperidin-1-yl)-5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (Int. B)**. To a magnetically stirred solution of ester Int. A (0.625 g, 1.38 mmol) in methanol (7 mL) was added a solution of potassium hydroxide (0.155 g, 2.76 mmol) in methanol (5 mL). The mixture was heated under reflux for 3 h. The cooling reaction mixture was then poured into water (10 mL) and acidified with 10% hydrochloric acid. The precipitate was filtered, washed with water, and dried under vacuum to yield the corresponding acid as a solid.

A solution of the crude acid (0.585 g) and thionyl chloride (0.492 g, 4.14 mmol) in toluene (10 mL) was refluxed for 3 h. Solvent was evaporated under reduced pressure, and the residue was then redissolved in toluene (20 mL) and evaporated to yield the crude carboxylic chloride as a solid. A solution of the above carboxylic chloride (1.24 mmol) in dichloromethane (5 mL) was added dropwise to a solution of 1-aminopiperidine (0.21 mL, 1.92 mmol) in dichloromethane (5 mL) at 0 °C. After stirring at RT for 3 h, the reaction mixture was added with brine and extracted multiple times with dichloromethane. The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. Purification by flash column chromatography on silica gel gave the expected amide Int. B.

Method B: Alternate Route for 5-Substituted Analogs



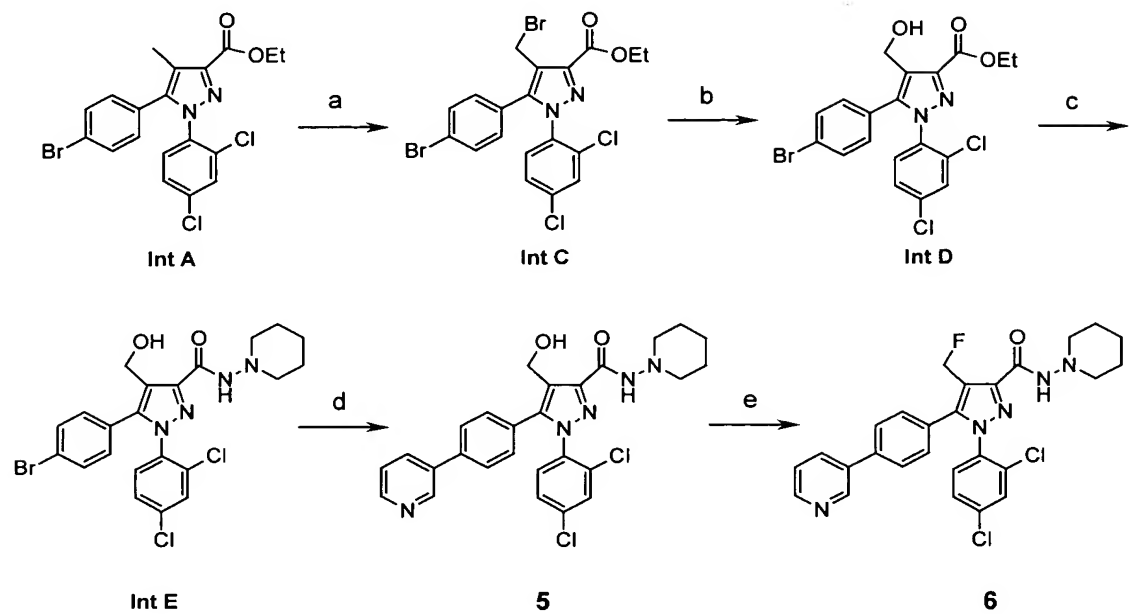
Some of the 5-substituted analogs can be prepared from Int. B via a Suzuki coupling reaction. The Suzuki coupling reaction allows synthesis of novel compounds in which the 5-phenyl ring is substituted with an aromatic ring or a heteroaromatic ring.

The coupling of a saturated heterocyclic ring (for example, morpholine) on the 5-phenyl ring can be obtained by Pd-catalyzed amination reaction (J. Org. Chem. 2000, 65, 1144-1157).

General procedure for the Suzuki Coupling reaction:

To a degassed solution of Int. B (100 mg, 0.197 mmol) and Pd $(PPh_3)_4$ (0.0085 mmol, 5 mol%) in 2 mL of DME was added 0.218 mmol of diethyl (3-pyridyl) borane or other aromatic boranic acid followed by 0.22 mmol of Na_2CO_3 in 1 mL of water. The resulting mixture was refluxed overnight. After reflux the mixture was diluted with CH_2Cl_2 and water. The organic phase was separated, and the water layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. Purification by flash column chromatography on silica gel gave the expected product.

Method C: Modification at Pyrazole Position 4



(a) NBS, AIBN, CCl_4; (b) $AgNO_3$, aq. acetone; (c) $AlCl_3$, 1-aminopiperidine, 1, 2-dichloroethane; (d) $Pd(PPh_3)_4$, diethyl (3-pyridyl) borane, DME, aq. $NaCO_3$; (e) DAST, CH_2Cl_2

These are obtained by functionalizing the 4-methyl group of the parent compound (Int. A). A variety of novel compounds having different substituents at pyrazole position 4 can be obtained. Similarly, modifications at pyrazole positions 3 and 5 can be obtained as shown under Method C.

Int. C. To a magnetically stirred solution of Int. A (2.02g, 4.44 mmol) in carbon tetrachloride (30 mL) was added *N*-bromosuccinimide (0.87 g, 4.89 mmol) and 2,2'-azobisisobutyronitrile (AIBN, 10 mg). The resulting mixture was refluxed for 3 h. After cooling to RT, the precipitate was filtered. The solvent was removed from the filtrate under reduced pressure to give the title product.

Int. D. To a magnetically stirred solution of silver nitrate (2.65g, 15.6 mmol) in 100 mL of 50% aqueous acetone at RT was added a suspension of Int. C (2.36g, 4.43 mmol) in 70% aqueous acetone. The mixture was stirred at 60 °C

overnight. After cooling to RT, the insoluble material was filtered off and the filtrate was concentrated under vacuum to evaporate acetone. The residue was extracted with CH_2Cl_2. The organic layer was washed twice with water, dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel gave the title product.

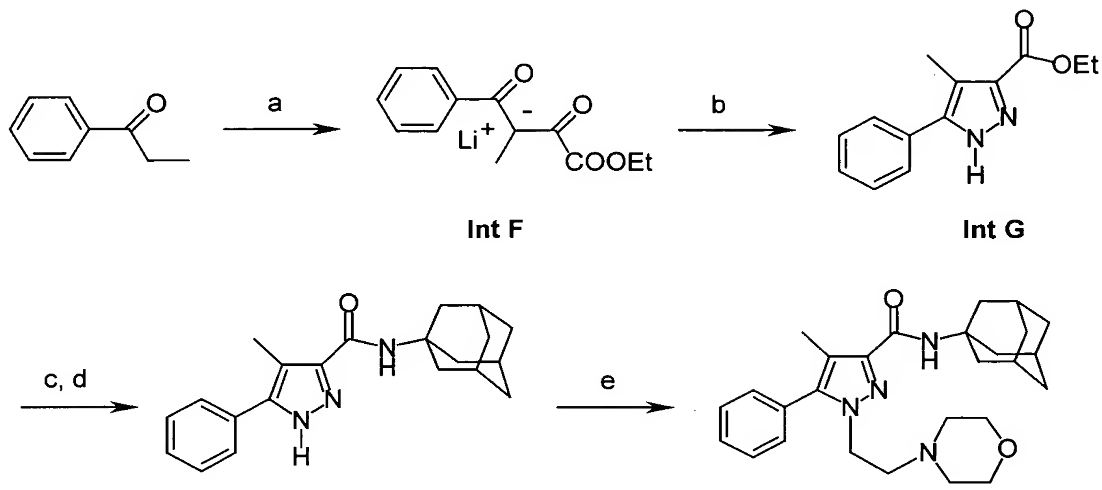
Int. E. To a magnetically stirred suspension of $AlCl_3$ (1.16g, 8.62 mmol) in 1,2-dichloroethane (20 mL) in an ice bath was added 1-aminopiperidine (2.0 mL, 18.0 mmol) in 1,2-dichloroethane (5 mL). The suspension was allowed to warm to RT. The solution of Int. D (2.03g, 4.43 mmol) in 1,2-dichloroethane (5 mL) was added into the above suspension and the mixture was stirred at RT for 2 h before quenching with a mixture of ice and H_2O. The mixture was stirred for a further 0.5 h and the resulting suspension was filtered through Celite and the organic phase separated. The aqueous phase was extracted multiple times with CH_2Cl_2 and the organic phases combined, washed with H_2O, brine, dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel gave the title product.

Compound 1-5. Compound 1-5 was obtained from Int. E using a Suzuki coupling reaction as described above.

Compound 1-6. To a magnetically stirred solution of compound 1-5 (30 mg, 0.057 mmol) in 1.5 mL of CH_2Cl_2 at 0 °C was added DAST. After 1h, the reaction mixture was poured into saturated $NaHCO_3$ (2 mL) and was extracted with CH_2Cl_2. The organic phases combined, washed with H_2O, brine, dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel gave the title product.

An alternate method for obtaining analogs with 1-alkyl substituents is described under Method D.

Method D: Modification at Pyrazole Position 1



Int F Int G

Int H 7

(a) LiHMDS, ether, then EtO_2CCO_2Et; (b) Hydrazine hydrochloride, EtOH; (c) KOH/MeOH; HCl/H_2O (d) $CO(imid)_2$/DMF, 1-adamantanamine; (e) NaH/DMF, 4-(2-chloroethyl)morpholine.

Int. F. To a magnetically stirred solution of lithium bis(trimethylsilyl)amide (40 mL, 1.0 M solution in hexane, 40 mmol) in diethyl ether (120 mL) was added a solution of propiophenone (5.30 g, 40 mmol) in diethyl ether (50 mL) at –78 °C. After the mixture was stirred at the same temperature for additional 45 min, diethyl oxalate (6.4 mL, 47 mmol) was added to the mixture. The reaction mixture was allowed to warm to room temperature (RT) and stirred for 16 h. The precipitate was filtered, washed with diethyl ether, and dried under vacuum to afford the lithium salt (Int. F).

Int. G To a magnetically stirred solution of the above lithium salt (7.58 g, 32 mmol) in 250 mL of ethanol was added hydrazine hydrochloride (2.4 g, 35 mmol) at room temperature. The resulting mixture was stirred at room temperature for 20 h. After stirring the solvent was removed under reduced pressure and the mixture was added with brine and extracted multiple times with dichloromethane. The combined extracts were washed with brine, dried over

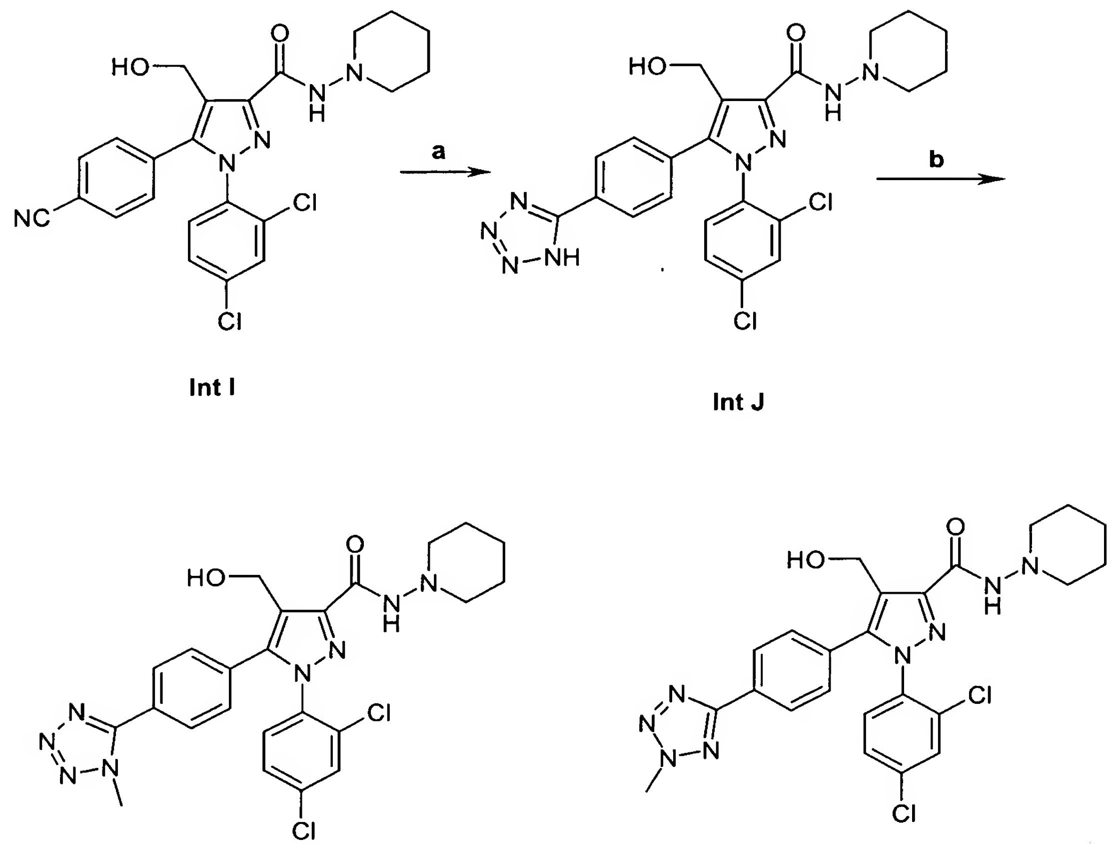
anhydrous sodium sulfate, filtered, and evaporated. Purification by flash column chromatography on silica gel gave the expected ester (Int. G).

Int. H To a magnetically stirred solution of ester Int. G (5.88 g, 26 mmol) in methanol (150 mL) was added 10% aqueous potassium hydroxide (36 mL, 64 mmol). The resulting mixture was heated under reflux for 3 h. The cooling reaction mixture was then poured into water and acidified with 10% hydrochloric acid. The precipitate was filtered, washed with water, and dried under vacuum to yield the corresponding acid as a solid.

To a magnetically stirred solution of the above acid (4.02 g, 16 mmol) in 45 mL of DMF was added 1,1'-carbonyldiimidazole (2.8 g, 17 mmol) in one portion at RT and the mixture was stirred at 60 °C for 3 hrs. To the above mixture was added a mixture of 1-adamantanamine (2.6 g, 17 mmol) in 45 mL of DMF. The resulting mixture was heated at 60 °C overnight. DMF was removed under reduced pressure. Ethyl acetate was added to the residue, and the mixture was filtered to collect the solid.

Compound 1-7. To a magnetically stirred solution of Int. H (188 mg, 0.56 mmol) in 4 mL of DMF, was added NaH (60% dispersion in mineral oil, 35 mg, 0.87 mmol) at 0 °C and the mixture was stirred at RT for 3 hrs. After stirring, the reaction mixture was cooled to 0 °C and a solution of 4-(2-chloroethyl)morpholine (185 mg, 1.25 mmol) in 1 mL of DMF was added. The resulting mixture was heated at 60 °C for 3 hrs. After heating, brine was added to the mixture, which was subsequently extracted multiple times with dichloromethane. The combined extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated. Purification by flash column chromatography on silica gel gave the expected product.

<u>Method E: Modification at Pyrazole position 5</u>



Int I Int J 2-5 2-6

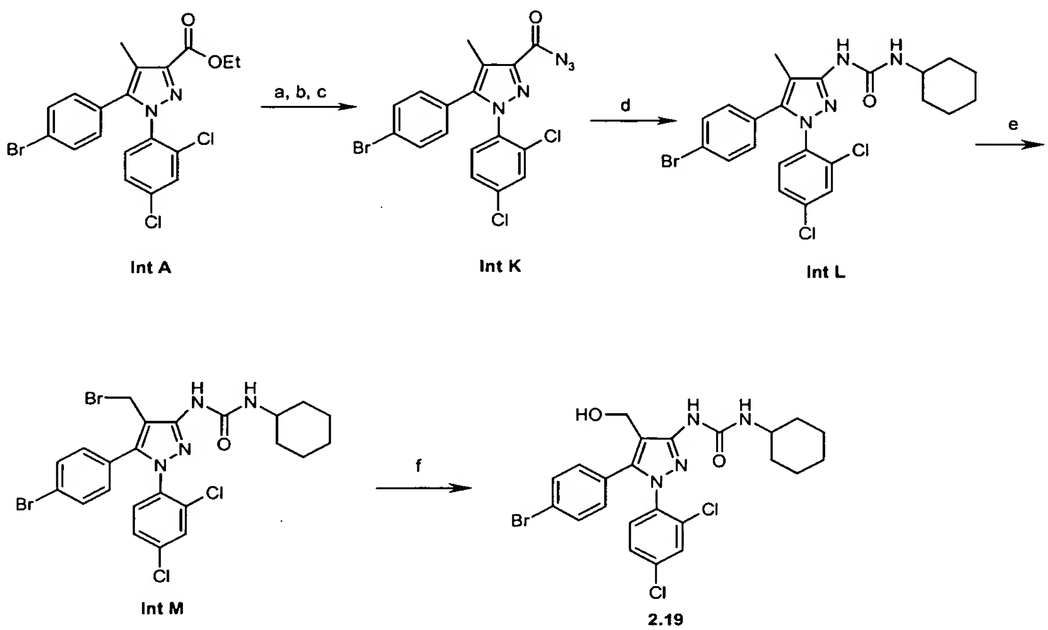
(a) NaN_3, $Et_3N.HCl$, toulene; (b) CH_3I, K_2CO_3, CH_3CN

Int. J. The mixture of Int I (1.50g, 3.19 mmol), NaN_3 (0.65g, 10 mmol) and $Et_3N.HCl$ (1.37g,10 mmol) in toluene (25 mL) was heated to 70 °C for 12h with stirring. After cooling, the product was extracted with water. The aqueous layer, 36% HCl was added dropwise to salt out the title product. After filtration, the solid was dried under reduced pressure. (see Synthesis, 6, 1998, 910).

Compounds 2-5 and 2-6. To the Int J (0.51g, 1 mmol) in CH_3CN (10 mL) K_2CO_3 (0.13g, 1 mmol) was added. To this CH_3I (0.12 ml, 2 mmol) was added. The contents were stirred at room temperature for 4-5 hrs. The reaction was quenched with water and extracted with ethyl acetate. The organic layer was separated and dried over anhydrous $MgSO_4$. The solvent was removed under

reduced pressure. Two isomers **2-5** and **2-6** were separated and purified by flash column chromatography on silica gel.

Method F: Modification at Pyrazole position 3



(a) KOH/MeOH, HCl/H_2O; (b) $SOCl_2$, toulene; (c) aq.NaN_3, THF; (d) cyclohexylamine, toulene; (e) NBS, AIBN, CCl_4; (f) $DMSO/H_2O$

Int. K. To a magnetically stirred solution of ester Int. A (0.625 g, 1.38 mmol) in methanol (7 mL) was added a solution of potassium hydroxide (0.155 g, 2.76 mmol) in methanol (5 mL). The mixture was heated under reflux for 3 h. The cooling reaction mixture was then poured into water (10 mL) and acidified with 10% hydrochloric acid. The precipitate was filtered, washed with water, and dried under vacuum to yield the corresponding acid as a solid.

A solution of the crude acid (0.585 g) and thionyl chloride (0.492 g, 4.14 mmol) in toluene (10 mL) was refluxed for 3 h. Solvent was evaporated under reduced pressure, and the residue was then redissolved in toluene (20 mL) and evaporated to yield the crude carboxylic chloride as a solid. To the solution of above carboxylic chloride (1.24 mmol) in THF (5 mL), NaN_3 (0.081g, 1.24 mmol) in 0.5mL of water was added at 0°C. The contents were stirred at that temperature for I hr. The reaction was quenched with water (5 mL), both aqueous and organic layers were separated. The organic layer was extracted using ethyl acetate (10

mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to give the title product.

Int. L. To a magnetically stirred solution of Int. K (0.448 g, 1 mmol) in toluene (10 mL) cyclohexyl amine (0.34 mL, 3 mmol) was added. The contents were stirred at 100°C for 8h. After cooling to room temperature the reaction was quenched by water (5 mL). Both aqueous and organic layers were separated, the organic layer was dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure. Purification by flash chromatography on silica gel gave the title product.

Int. M. To a magnetically stirred solution of Int. L (0.522g, 1 mmol) in carbon tetrachloride (20 mL) was added *N*-bromosuccinimide (0.21g, 1.2 mmol) and 2,2'-azobisisobutyronitrile (AIBN, 5 mg). The resulting mixture was refluxed for 3 h. After cooling to RT, the precipitate was filtered. The solvent was removed from the filtrate under reduced pressure to give the title product.

Compound 2-19. To the Int. M (0.601g, 1 mmol), DMSO/H_2O (5:1) were added. The mixture was stirred at 60 °C for 5h. After cooling to RT, water (30 mL) was added. The organic layer was extracted with ethyl acetate and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel gave the title product.

11 rats were trained to press a lever five times to receive a 45 mg food pellet. The training continued over a time period of several weeks. After the training period all rats received drug treatments once per week. The specific rat receiving a drug treatment and the dosage given were each randomly varied. The treatments comprised administration of a vehicle control solution or various dosages of inventive compound 1-5 in combination with the vehicle control solution. All injections were given IP. Ten minutes after injection the rat was placed in proximity to the lever.

Figure 1 illustrates a mean (±SEM) number of lever presses in 30 min for treated animals. The overall suppression of food-reinforced lever pressing was

statistically significant ($p<0.05$). Figure 1 illustrates a classic dose response curve wherein as the dose of drug (inventive compound 1-5) increases, lever pressing consistently decreases. Without wishing to be bound to any theory, applicants believe that inventive compound 1-5 antagonizes (blocks) the CB1 receptors, thereby suppressing appetite and leading to decreased lever pressing.

Those skilled in the art will recognize, or be able to ascertain with no more than routine experimentation, many equivalents to the specific embodiments of the invention disclosed herein. Such equivalents are intended to be encompassed by the scope of the invention.